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REVIEW ARTICLE

A Fetoscopic Approach for Antenatal Correction of Open Spina Bifida

[1,2]Renato AM de Sá, [3]Gregório L Acacio, [4,5]Denise AL Pedreira

ABSTRACT

Since the advent of fetoscopy, a paradigm shift toward minimally invasive options for antenatal open spina bifida (OSB) correction has been witnessed, resulting in rapid technological innovations and improved outcomes for both the mother and fetus. A history of the minimally invasive surgical management of OSB is presented, with a focus on a novel Brazilian fetoscopic approach.

Keywords: Fetal therapy, Fetoscopy, Meningomyelocele, Myelomeningocele, Spina bifida.

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INTRODUCTION

Fetoscopic surgery owes much of its history to the development of endoscopic techniques, which arose in response to peoples' inherent curiosity of and desire to inspect the concealed cavities of the human body. Many historians credit the Arabian physician Albukasim (936–1013 AD) with being the first to use reflected light to inspect an internal organ.[1]

However, the ideas that formed the framework for fetoscopic surgery were not initially reported until 50 years ago. Fetoscopy procedures originated with Westin in 1954,[2] who introduced a 10-mm-diameter hysteroscope through the uterine cervix of patients who were to have therapeutic abortions at 14 to 18 weeks. The transabdominal technique was then introduced by Mandelbaum et al[3] in 1967 during attempts at intrauterine fetal transfusion for hemolytic disease. In 1972, Valenti[4] obtained fetal skin samples prior to the termination of pregnancy using a 5 mm needle scope, which he called an endoamnioscope. It was not until 1973, however, that the term "fetoscopy" was introduced by Scrimgeour,[5] who exposed the uterus during a laparotomy and introduced a 2.2 mm needle scope to view the amniotic cavity and fetus.[2]

Fetoscopic techniques have continued to develop following these early advancements. After considerable experience with guided laser occlusion of chorioangiopagous vessels for the treatment of the Twin-to-Twin-Transfusion Syndrome, and Management of Myelomeningocele Study (MOMS) trial results demonstrating the benefits of prenatal over postnatal correction regarding postnatal neurological outcomes,[6] Pedreira et al[7] reported the antenatal correction of open spina bifida (OSB) using a fetoscopic approach and a simplified closure technique. In this study, four fetuses with lumbosacral defects were operated on *in utero* at 25 to 27 weeks. Specifically, percutaneous surgeries were performed under general anesthesia using three trocars and partial carbon dioxide insufflation.[7] Ten consecutive pregnancies with lumbosacral OSB were also enrolled in the CECAM trial, a phase one human trial for the fetoscopic correction of OSB.[8]

Frontiers of Antenatal Surgery

Fetoscopic surgery for the treatment of OSB brings new and unknown possibilities to the treatment of congenital defects. Thus, the following three points must be taken into account when looking to expand the frontiers of antenatal surgery. Firstly, fetoscopic surgery should be performed only when it is possible to do so as safely, as thoroughly, and for the same indications as for the open technique.[6] Fetal surgery is a highly complex surgical intervention for repairing birth defects in the womb, and therefore requires the utmost expert care for both the mother and unborn baby. Furthermore, fetoscopic surgery can only be successfully performed when the required technology is currently available. Secondly, fetoscopy permits an exceptional view of the uterine environment, potentially enabling the more effective diagnosis and treatment of congenital defects. However, while new surgical

[1,2]Clinical Research Unit, Fernandes Figueira Institute – Fiocruz Pós Graduação em Ciências Médicas, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

[3]Department of Obstetrics, University of Taubaté, Taubaté Brazil

[4,5]Department of Pathology, University of Sao Paulo; Fetal Therapy Center, Albert Einstein Hospital, São Paulo, Brazil

Corresponding Author: Renato AM de Sá, Pós Graduação em Ciências Médicas, Federal Fluminense University, Rua Mário Alves 69, 1204, Niterói, Rio de Janeiro, Brazil – 24220-270 Phone: 5521982093999, e-mail: renatosa.uff@gmail.com

techniques allow a minimally invasive approach to be used for fetoscopic intervention, there is still much more clinical experience with open surgery for the antenatal repair of OSB. On the other hand, open surgery has the disadvantage of presenting a greater risk of hysterotomy outside the uterine segment to the mother.[8] The benefits and costs of fetoscopy must therefore be carefully considered. Thirdly, fetoscopy must not be considered the opposite of classic surgery for OSB. Indeed, fetoscopy is not a different type of surgery; it is only another surgical technique that takes a less invasive approach.

Origin of the Fetoscopic Approach

Bruner et al1[10] performed the first *in utero* endoscopic coverage of fetal open myelomeningocele in 1994, reporting the technical feasibility of endoscopic intrauterine skin graft placement over surgically induced defects, including an overexposed spinal cord, in a sheep model. These grafts successfully excluded amniotic fluid from the underlying lesion and provided a matrix for fetal skin growth below the graft.

In Brazil, the Pedreira group[11] developed a surgical technique whereby a fetoscopic approach was used for the treatment of skin burns. This approach utilized bacteria-produced biosynthetic cellulose, a low-cost product that can act as the duramater in animal models and humans.[12,13] After extensive laboratory experiments in rabbits and sheep, and careful microscopic evaluation of the spinal cord in these animals, it was shown that biosynthetic cellulose could complete the duramater and self-healing, that could lead to a definitive correction of the defect. This was achieved with the additional benefit that the cellulose itself would keep the spinal cord apart from the skin.[13-15]

Following these experiments, the next step was to develop an alternative way to keep the cellulose in place when correcting a large defect. In approximately 20 to 30% of fetuses in which prenatal correction of OSB is carried out, direct skin closure is not possible. Promisingly, it has been shown that the placement of a bilaminar artificial skin (a silicone and an acellular dermal matrix layer) over a cellulose graft can successfully keep the graft in place without necessitating a change in surgical techniques used.[16] In particular, it was observed that not only was the dermal matrix repopulated, but also that a neoepidermis was produced on top of it. This led the authors to conclude that a new skin had formed over the cellulose graft, thereby protecting it from dislodgement.[16]

Growth and Adoption of the Fetoscopic Approach (SAFER technique)

In 2006, Kohl et al published a case series of the first three surgeries in humans involving percutaneous fetoscopic patch coverage of OSB. The procedure in these initial cases was not fully effective as postnatal neurosurgical correction was required.[17] With subsequent revision of the surgical technique used, Kohl then retrospectively analyzed the cases of 51 patients who had undergone the procedure at his center between July 2010 and June 2013. For these patients, the mean maternal age at surgery was 31.5 years and mean gestational age at surgery was 23.7 weeks. It was reported that the fetoscopic surgery resulted in no uterine dehiscence or rupture, no spontaneous labor, and no placental abruption. Blood transfusion was also not required, and gestational age at delivery in survivors ranged from 27.9 to 38.1 (mean = 33.0) weeks.[18]

At the same time in Brazil, Pedreira et al[8] had just concluded a phase one human trial using the alternative skin-over-cellulose technique and partial carbon dioxide insufflation. Using this newly named *S*kin-over-biocellulose *A*ntenatal *Fe*toscopic *R*epair (SAFER) technique, ten consecutive pregnancies with lumbosacral OSB were enrolled in this study, with a median gestational age at time of surgery of 27 weeks (range = 25–28 weeks). Endoscopic repair was completed in 8/10 fetuses, with two cases being unsuccessful due to loss of uterine access. The mean gestational age at birth was 32.4 weeks with a mean latency of 5.6 weeks between surgery and delivery (range = 2–8 weeks).

It was found that of the seven infants available for analysis, complete reversal of hindbrain herniation occurred in six babies. Functional motor level was also the same or better than the anatomical level in 6/7 cases, though three babies required ventriculoperitoneal shunting or a third ventriculostomy. Furthermore, there was no significant maternal morbidity and no evidence of myometrial thinning or dehiscence. However, surgeries were complicated by premature membrane rupture and premature delivery.[5]

The surgical approach undertaken in Brazil represents more than a decade of animal work and more than two decades of operative fetoscopy experience.[7,8,14-17] With this approach, percutaneous fetoscopic surgery for OSB is performed via three or four trocars. Using the Seldinger technique, vascular introducers and a balloon-tipped laparoscopic trocar are placed into the amniotic cavity under continuous ultrasound monitoring. Once the amniotic fluid is partially removed, partial amniotic carbon dioxide insufflation is performed as described by Kohl et al.[17,18]

Fetal posturing is then carried out by fetoscopic instruments to move the fetus into a position in which the malformation can be reached during surgery. The neural placode is dissected with a circumferential incision at the transition zone. The neural cord is subsequently covered with a biocellulose patch (Bionext, Paraná, Brazil) and the skin closed over the patch with a single running stitch. If the defect is too large, a skin substitute (Integra®, Plainsboro, USA) is placed over the biocellulose patch for two-layer closure of the defect. Following coverage of the lesion, the insufflated carbon dioxide is removed with simultaneous refilling of the amniotic cavity.[8]

FUTURE DIRECTIONS

With the help of improved imaging modalities, it has become possible in recent years to prenatally diagnose OSB as early as the first trimester. Considerable advances have also been made in preventing neural tube defects through folic acid supplementation. Despite this progress, OSB still affects approximately 1 in 3,000 live births, which translates to 1,500 live-born infants with this congenital defect each year in the USA[19] and 1.4:1,000 live births in Brazil.[20] The defect results in injury of spinal cord tissue at the level of the bone lesion, as well as hindbrain herniation. Depending on the level, OSB also results in varying degrees of lower extremity paralysis, bladder and bowel incontinence, sexual dysfunction, and orthopedic disabilities.

While initial attempts to treat OSB using a fetoscopic approach were not encouraging,[21] novel techniques can be performed in human fetuses with a high rate of technical success and a low rate of perioperative mortality.[8,18] With increasing clinical experience, fetoscopic surgery can be performed in most cases regardless of placental position. Indeed, during ultrasound-guided trocar insertion in cases with an anterior placenta, a safety margin of about 3 cm from the placental edge suffices in preventing placental injury.[18]

The development of fetoscopic approaches for fetal OSB surgery may also permit prenatal coverage of the lesion much earlier in gestation. There is a growing body of literature supporting the therapeutic potential of using a tissue engineering approach to promote tissue coverage of the defect, possibly by introducing engineered tissue through a needle under ultrasound guidance.[21]

Despite the progress that has occurred so far, advances in instrumentation and image transmission are far from complete. Developments in these areas may allow open surgery to be replaced with fetoscopic intervention, hopefully resulting in less discomfort, shorter hospital stays, faster rehabilitation for the mother, and a lower risk of maternal morbidity. On the other hand, there are some costs associated with a fetoscopic approach, including longer operating times, higher instrument costs, and a possible need for postnatal neurosurgical intervention. Therefore, we must ask the question of whether it is worthwhile to carry out procedures by fetoscopy rather than by open surgery. In order to decrease the risks to the mother and fetus, and to improve surgical outcomes, rigorous experimental testing and comparisons with open surgery techniques will be required to evaluate the risks and benefits of any new approaches.

Although we believe that fetoscopic repair of OSB should be tested in a randomized study, we understand that one of the difficulties of proposing such study is the different fetal repair techniques that are currently been used in this two approaches and that maybe one can start using the fetoscopic technique in cases where there is a maternal contraindication for the open surgical approach, for example, in case of a previous c-section or in the presence of an uterine scar.

CONCLUSION

If the lessons of the past are any indication, it is clear that surgical fetal interventions will continue to advance in the direction of minimally invasive procedures. In keeping with the principles of minimally invasive surgery, advances in fetoscopic OSB surgery aim to improve maternal outcomes (i.e., postoperative intensive care management, length of hospital stay, risk of uterine rupture, and cosmetic appearance) while demonstrating equivalent fetal outcomes, as well as technical feasibility, safety, and reproducibility.

In the five years since MOMS trial results were published, we have witnessed a paradigm shift in the management of OSB. If the reversal of hindbrain herniation without direct closure of the duramater can be shown in larger numbers, there will be a change in the neurosurgical approach to OSB. Furthermore, the advent of fetoscopic surgery for OSB has resulted in broad implications that transcend OSB intervention and have helped shape the landscape of modern minimally invasive fetal surgery.

However, despite the increasing interest in minimally invasive fetal surgery, the fetoscopic approach has been slow to gain universal adoption. Although it has been shown to be an effective and safe option for the management of OSB, the preterm premature rupture of the membrane remains a significant complication.[8] To thoroughly evaluate the potential of fetoscopic procedures in various fields of fetal surgery, it is imperative that experimental testing and comparisons with open surgery techniques be required.

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