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Endoscopic fetal surgery for neural tube defects

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A B S T R A C T

Prenatal repair of open spina bifida reduces shunt rates and may improve postnatal motor and neurodevelopmental outcomes. The hysterotomy required for the open fetal surgery leaves subsequent pregnancies at risk of uterine rupture. Hysterotomy site rupture confers significant morbidity and mortality risks for both mother and fetus. Fetoscopic repair is feasible and seems to achieve at least the same, postnatal neurological outcomes as those of the open repair. Fetoscopy can be accomplished by a laparotomy-based approach, or it can be entirely percutaneous. Thus far, the laparotomy-based approach leads to less PPROM and higher gestational age of delivery than the percutaneous-based one. However, the percutaneous approach is being modified, and outcomes are continuing improving, now delivery reached 35 weeks. Surgical techniques for the repair of the defect are not yet standardized, and the type of defect repair may affect long-term outcomes, especially regarding neurogenic bladder and cord tethering. The role of open fetal surgery in the management of spina bifida may be restricted to selected cases in the near future.

Critical appraisal of benefits and risks of fetal surgery

The results of the randomized controlled trial MOMS seem to have changed the timing of open spina bifida (OSB) repair from the postnatal to the prenatal period. The trial was interrupted owing to better efficacy in the group submitted to prenatal repair than the group submitted to postnatal repair.

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Table 1
Main surgical and perinatal outcomes of open spina bifida repair reported in the literature since the MOMS trial.

	Open surgery MOMS	Open surgery CHOP pos-MOMS	Fetoscopy percutaneous Germany	Fetoscopy percutaneous[a] Brazil	Fetoscopy laparotomy-assisted[a] USA	Open surgery MOMS
Timing OSB repair	POSTNATAL	Prenatal	Prenatal (Post-MOMS)	Prenatal	Prenatal	Prenatal
Author	Adzick et al., 2011	Adzick et al., 2011	Moldenhauer et al., 2015	Graf et al., 2017	Lapa et al., 2018	Belfort et al., 2017
Number of patients	80	78	100	71	47	28
Perinatal mortality	3% (2/80)	3% (2/78)	6% (6/98)	NA	4.4% (2/45)	0
Intraoperative failed repair/Aborted procedure	0	0	0	16 (3/19)[c]	4.3% (2/47)	21% (6/28)
Total PPROM	8% (6/80)	46% (36/78)	32% (31/96)	84% (43/51)[b]	84% (38/45)	23% (5/22)
PPROM ≤34+0w	NA	NA	NA	NA	78% (35/45)	14% (3/22)
Mean GA at birth	37.1	34.1 ± 3.1	34.3	32.9 ± 2.7	32.8 ± 2.5	38.5 ± 1.2
Delivery <30 + 0 weeks	0	13% (10/78)	9% (9/96)	13% (9/71)	16% (7/45)	5% (1/22)
Delivery >34+0w	95% (76/80)	54% (42/78)	54% (52/96)	24% (17/71)	29% (13/45)	77% (17/22)
Complete reversal of Chiari II malformation at 1 year	4% (3/69)	36% (25/70)	71% (59/83)	NA	68% (19/28)	41% (9/22)
Shunt rate at 1 year	82% (31/40)	40% (66/82)	NA	45% (32/71)	47% (20/43)	41% (9/22)
Neonatal better than predicted motor by anatomical ≥1 myotome	23% (14/67)	44% (27/62)	53% (44/83)	NA	56% (23/41)	NA
Postnatal any additional SBA repair	6% (5/80)	13% (10/77)	1% (1/83)	28% (20/71)	18% (8/45)	36% (8/22)
CSF leak	NA	NA	NA	35% (7/20)	18% (8/45)	32% (7/22)

[a] Including learning curve data.
[b] Degenhart et al., 2014.
[c] Verbeek et al., 2011.

At 12-months and 30-months of follow-up, the prenatal group showed significant motor improvement with 50% more ambulation and 50% decrease of need for shunt placement than the postnatal repair group (Table 1). Although the 30-month follow-up failed to show maintenance of benefits in cognitive development and no improvement in bladder function, there is general agreement that fetal repair should be offered in selected cases. However, because of the open fetal surgery access used in the MOMS trial, these favorable outcomes occurred at the expense of mothers who were at an increased risk of uterine dehiscence and rupture, as well as other morbidities.

Emerging evidence of the obstetric risks in subsequent pregnancies after open fetal surgery shows 9–14% risk of uterine rupture in early third or second trimester, followed by up to 50% risk of fetal death. Other potential disadvantage is that iterative c-section is mandatory in future pregnancies, which can limit the offspring (Table 2).

The selection criteria for fetal repair need to be carefully established owing to the delicate balance between fetal benefits and maternal risks. Particularly in the MOMS trial, the inclusion criteria were highly selective, and only one third of patients ended up to be eligible for fetal repair. The development of a safer minimally invasive technique can increase the number of patients to be eligible and benefit more OSB-affected fetuses.

Timing of repair

The MOMS study showed objective benefits, but the same neurosurgical repair technique was used in both the prenatal and the postnatal period. Therefore, it is highly possible that it was not only the surgical repair technique that proved to be beneficial but also the prenatal timing of the treatment. From this perspective, a new question emerges, which we address in the following sections.

The upper limit for open surgery repair was limited owing to the lack of evidence of significant neurological improvement after 26 weeks of pregnancy, because it needs to be balanced against the maternal risks. This concept can also be challenged if a safer maternal approach becomes an option.

The MOMS recruitment and completion took more than 10 years from its conception in the early 2000s. Therefore, different surgical techniques and patches became available during this period, and currently, the three-layer neurosurgical repair is no longer in use by one of the main groups involved in the trial. Instead, a two-layer repair including a modified bilateral myofascial flap has been used successfully, and it results in better main outcomes than those reported in the MOMS trial (Table 1).

Operative access and safety of carbon dioxide

Bruner and Tulipan et al. made the first attempts for prenatal repair of OSB using fetoscopy. They were followed by Farmer et al., but owing to technical difficulties and poor perinatal outcome, both groups abandoned the fetoscopic approach in favor of open fetal surgery.

Nevertheless, other groups kept pursuing fetoscopy, and currently, two types of fetoscopic approaches are available: the entirely percutaneous and the laparotomy assisted. In the entirely percutaneous approach (see Figs. 1 and 2), no laparotomy is needed; the trocars are placed through the

Table 2
Differences between open fetal surgery and c-section.

	Open fetal surgery	C-section
Mode of delivery	C-section mandatory	vaginal allowed
Labor	never allowed	allowed
Vaginal delivery	never allowed	allowed
Uterine rupture timing	late second trimester	late third trimester
Uterine rupture	spontaneous	during labor
Fetal death	~50%	rare
Incidence	~10%	~4%

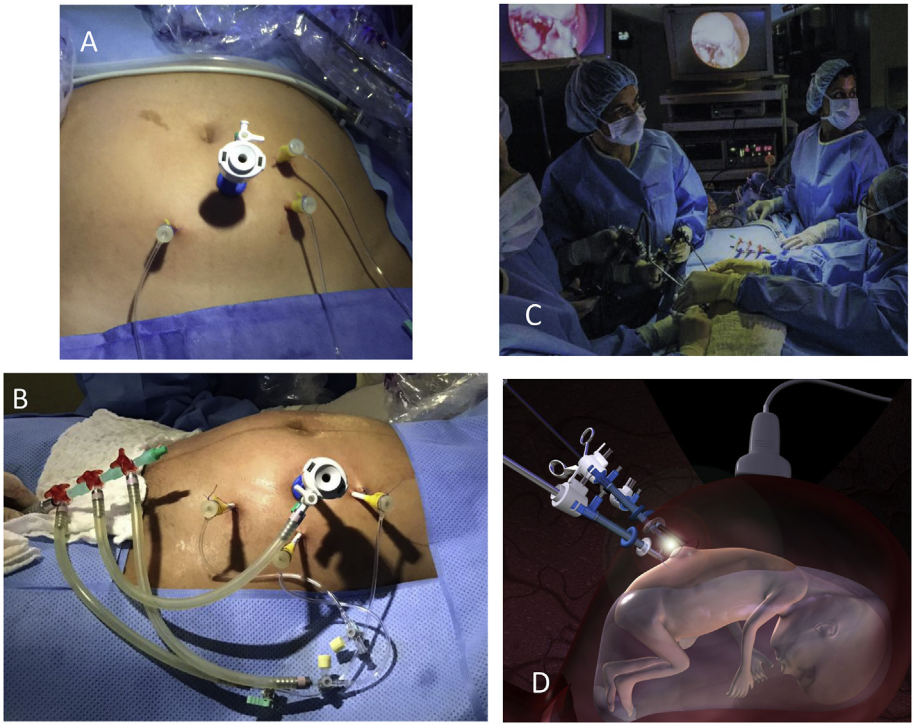

Fig. 1. Trocar placement in the entirely percutaneous approach. A. Setup in a case of posterior placenta. B. Setup in a case of anterior placenta; note that the four trocars are placed in the lateral uterine wall. C. External view of the OR during surgery. D. Schematics of the fetal repair.

abdominal and uterine wall under ultrasound guidance and the Seldinger technique. Maternal postoperative pain is minimal; tocolysis is usually not required, even in the immediate postoperative period; the average gestational age for delivery is 33 weeks, but the preterm premature rupture of the membranes (PPROM) rate approaches 80%. In the laparotomy-based approach, a wide laparotomy is needed, the uterus is entirely exteriorized, and smaller trocars are placed under direct visualization through the uterine wall. Maternal pain requires aggressive management after surgery, but gestational age of delivery reaches 37 weeks (Table 2).

Thomas Kohl was the pioneer in the development of the entirely fetoscopic approach, using partial carbon dioxide insufflation (PCI) to enhance manipulation and visualization. Since his first publication in 2006, his group has operated on more than 100 fetuses and published the results on the first 59 cases (Table 1).

His group was responsible for initially mitigating the fear of fetal acidosis, resulting in neurological damage subsequent to the use of CO_2. More recently, Baschat et al. showed no evidence of acidemia in human fetuses using PCI. No acidosis or hypoxemia was demonstrated in cord blood samples of three cases submitted to fetal repair, in up to 181 min of surgery.

The German experience was followed by the Brazilian group (Table 1). This group used the same PCI approach but a different neurosurgical repair based on the innovative use of a biocellulose patch, wich allows fetal self-repair. The analysis of the initial 47 cases proved that a primary watertight repair was achievable without a direct suture of the dura mater. The biocellulose patch induced the development of a neodura mater as a result of fetal wound healing. This finding could be

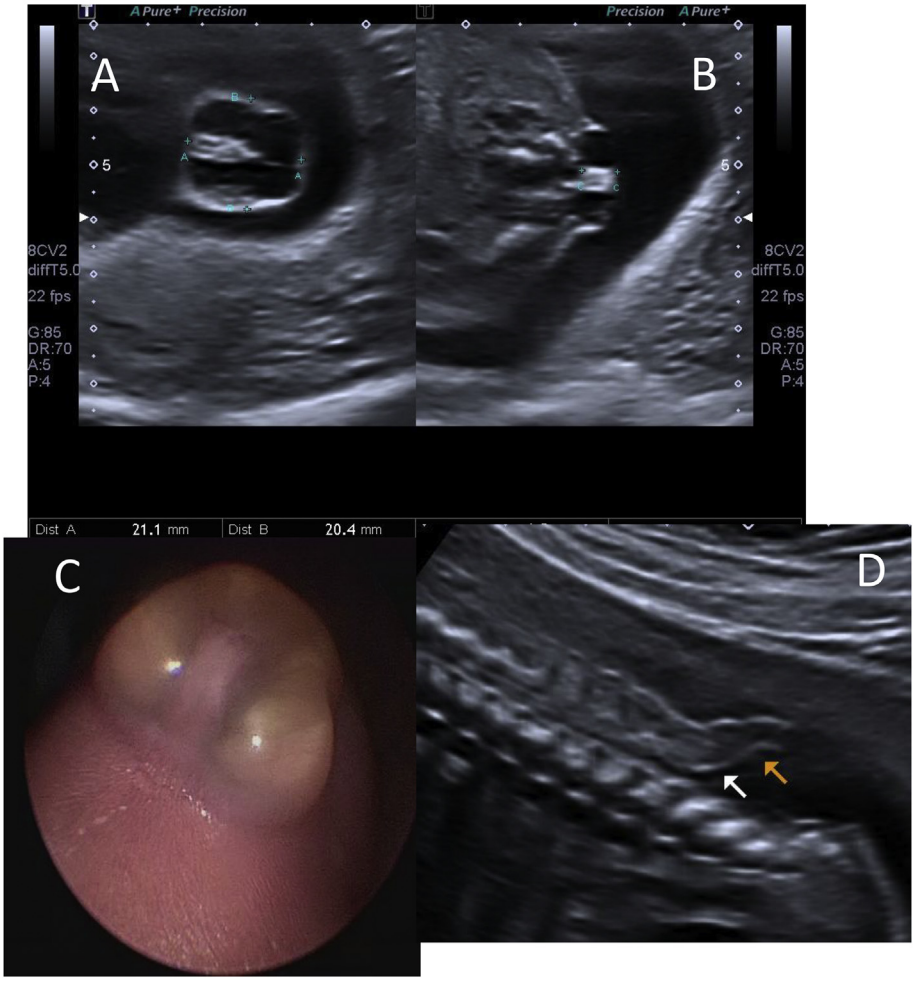

Fig. 2. Ultrasound images (A, B, and D) of a meningomyelocele defect at 26 weeks and the corresponding fetoscopic image of the defect (C).

documented by our better rates of prenatal reversal of hindbrain herniation and similar CSF leak from the lesion site than the MOMS trial (Table 1). Postnatal follow-up showed no acidosis-related anatomical abnormalities on imaging studies or acidotic encephalopathy that could be related to carbon dioxide-induced acidosis.

The Brazilian group was followed by Carrera and Guine in Barcelona, Peiro in Cincinatti, and Belfort in Houston; all groups used a two- or three-port laparotomy approach, in which a wide lower transverse laparotomy (abdominal muscle is usually sectioned) is performed, and the uterus is positioned outside the abdominal cavity for the direct view of trocar placement. Different sutures and patches have been used by these groups, and the results of the first 22 cases operated were published comparing an iterative and a standardized approach (Table 1). In this cohort, no acidosis-related injuries were demonstrated.

Comparison of standardized outcomes

Table 1 shows the main outcomes reported by the above-mentioned groups. Nevertheless, the use of different surgical techniques for the lesion repair, rather than the type or operative access, can be responsible for the main differences. That is why it is so important to understand the difficulties to standardize the repair technique.

Different neurosurgeons use different techniques and different patches for the postnatal OSB repair. As there is no universally accepted postnatal repair technique, the best technique for prenatal surgery is yet to be determined.

Many factors can explain the heterogeneity of the postnatal neurosurgical techniques. The lesions can be very different in size and shape; the availability of patches is not universal (some patches have very high costs); different countries can have different patches approved; neurosurgeons may have personal preferences.

After birth, the main goal of surgery may not be the preservation of the placode but rather to provide a watertight dura mater closure, as many believe the placode lesion is already established.

In the prenatal setting, the main goal may be considered the contrary of the postnatal repair. The primary goal of the antenatal repair is to preserve the neural elements by avoiding further neural damage to the exposed placode. We should keep in mind tha the initial idea underlying the proposal of fetal OSB repair was the preservation of the spinal cord from the progressive injury caused by the intrauterine environment. It was not foreseen that fetal OSB repair would also provide *in utero* watertight sealing, thereby promoting reversal of the hindbrain herniation.

Type of repair

For the prenatal repair, many different patches were studied during the last two decades. The patches varied not only in their nature (collagen-derived dermal matrix, synthetic materials, etc.) but also in anatomic placement, that is, sutured to the muscle/aponeurosis or to the skin, glued to the placode, under the skin, etc.

Our group chose to suture the skin above the biocellulose patch (one patch), and if there was not enough skin to be sutured in the midline, an artificial skin was used (two patches). The artificial skin has two-layers: a dermal matrix and a silicone layer designed to mimic the dermis and epidermis, respectively. This strategy to correct the large defects found in rachischisis was tested in animals before use in humans. Our team chose this approach instead of using “relaxing skin incisions,” a strategy successfully used after birth because, when large incisions are needed, the scar results are less than optimal, they may require plastic surgery limmiting the positioning of the baby and prolonging the neonatal stay.

Another potential advantage of the biocellulose patch is the possibility of reduction of tethered cord; there is a strong possibility that this may have a game-changing impact in the long-term outcome. Tethered cord is a late-onset complication occurring at 3–6 years of age, and it needs surgical intervention to release the placode adherence to the subcutaneous tissue scar. For the diagnosis of tethered cord syndrome, there has to be loss of any neurological function, that is, motor, urinary, fecal, change in gait, etc. Hence, there has to be loss of acquired neurological capabilities, that may return or not.

It is our understanding that new patches should be tested in an animal model and recommend that they are tested against the biocellulose, before the start of new clinical trials. The new patch should not only result in watertightness but also in neural preservation and lack of adherence to neural tissue. There is growing interest in the use of an umbilical cord-derived patch for the prenatal repair. This patch was tested in vitro against the biocellulose patch; unfortunately, the biocellulose was not applied underneath the skin, where it has been proven to induce the formation of a neodura mater. Instead, the biocellulose was sutured to the skin, which does not allow the neodura mater to be formed.

Percutaneous or laparotomy-assisted approach for fetoscopy?

Currently, the Achilles heel of the entirely fetoscopic approach is the 80% rate of PPROM and median gestational age of delivery of 32–33 weeks. In the laparotomy approach, PPROM is 40% and the average gestational age at delivery is 37 weeks. In favor of the entirely percutaneous approach is the repair technique that has been largely tested in animal models and has the potential of reducing neurogenic bladder and tethered cord. On the contrary, the laparotomy-assisted approach involves a repair technique that maybe is not the best for fetal repair. Contrary to the patch and glue technique developed initially by the group, the standardized technique was developed on a clinical basis, not tested in the animal model (see Table 3).

The gain of an average of 3–4 weeks in the gestational age of delivery using the laparotomy approach is very appealing, nevertheless 34 weeks was the mean for the MOMS trial. The occurrence of 32% CSF leak at birth in Belfort et al. series raises concerns because of the risks of a second neurosurgical intervention in the newborn. If the CSF is found to be leaking at birth, there is also the potential risk that a suboptimal reversal of hindbrain herniation has occurred. Comparing the two series, in the laparotomy-assisted approach, 57% of cases showed reversal of hindbrain herniation, while in the entirely percutaneous approach, it occurred in 90% of cases (Table 1).

The upper gestational age limit of 26 weeks is technically not an issue when using the percutaneous technique because the uterus does not need to be out of the abdominal cavity for the fetal repair. Nevertheless, this can be an issue for both open and laparotomy-based approaches.

Is a randomized trial to compare operative access justified?

The question about the need for a prospective randomized trial to validate the fetoscopic approach is a very important question. Is a randomized controlled trial comparing the open versus fetoscopic approach justified, if maternal safety is better and neurological outcomes are comparable between the groups? Furthermore, the MOMS trial repair technique has already been largely modified and continues to undergo modification. Some of these modifications are not suitable for the fetoscopic approach; hence, a comparison would be impossible. The challenges of conducting another trial in this area would be many and from an ethical point of view may be not justifiable.

In the meantime, the establishment of the best surgical technique for the fetoscopic repair of OSB should be the primary goal. Some changes in surgical protocol can also shift results toward favoring one or other technique. For instance, after our group started using the humidification of CO_2 during surgeries, the mean gestational age of delivery increased to 34.8 weeks and PPROM decreased to 40%, and no delivery occurred before 31 weeks.

International consortium for fetoscopic repair

To establish the best fetoscopic strategy, an International Consortium for the Study of Fetoscopic Spina Bifida Repair was formed in June 2017 (World Congress Fetal Medicine, Slovenia), under the

Table 3
Main differences in the postoperative period and perinatal outcomes among the three main approaches for fetal repair of OSB.

	Open fetal surgery	Fetoscopy laparotomy	Fetoscopy percutaneous
Analgesia after surgery	PCA	PCA	no
Tocolysis	yes	yes	no
Intensive care unit after surgery	always	always	rare
Discharge (days)	4–5	4–5	2–3
	strict bed rest	modified bed rest	modified bed rest
Mode delivery current pregnancy	C-section mandatory	vaginal allowed	vaginal allowed
Labor	never allowed	allowed	allowed
Subsequent pregnancy uterine rupture	10% (50% fetal death)	not reported	never occurred

auspices of the Fetal Medicine Foundation. The main goal of this consortium is to gather all groups and specialists interested in the fetoscopic approach to exchange personal experiences. Learning from each other, these groups can combine efforts to improve maternal safety and neurological outcomes. In addition, they may provide teaching and training for a safer introduction of this new technique in other fetal medicine centers worldwide.

Guidelines for clinical care

Percutaneous and laparotomy-assisted approaches for fetoscopy have demonstrated to achieve similar neurological outcomes (this is already known) as those observed in the MOMS trial, if not better (this is not yet known). The best technique for the defect repair is yet to be established, but a decrease in neurogenic bladder and tethered cord occurrence may be game-changing outcomes in such decision.

The risk of uterine rupture in future pregnancies should be emphasized during preoperative counseling for the open repair. The risk of uterine rupture leading to the loss of an otherwise-normal unborn child in a subsequent pregnancy reaches approximately 10%.

Patients submitted to open surgery should be educated about the symptoms of internal bleeding or hypovolemic shock, such as dizziness, tachycardia, or any abdominal discomfort. In such cases, they should be promptly clinically evaluated, preferably in the hospital where the planned delivery is scheduled, but the nearest possible.

Delivery should be planned for 37 weeks, and a resection of the uterine scar area may also reduce the risk of uterine rupture in subsequent pregnancies (not yet known).

While taking prenatal care of any patient submitted to an open fetal approach in a previous pregnancy, obstetricians must inform that they should avoid a subsequent pregnancy for at least two years because this seems to reduce the risk of uterine rupture (not yet known).

Summary

Prenatal repair of OSB substantially improves neurological outcomes. Currently, fetal repair is performed by open fetal surgery, which requires a hysterotomy. The hysterotomy leaves a uterine legacy that confers significant maternal and fetal morbidity and mortality risks for future pregnancies. Fetoscopic repair, either laparotomy assisted or entirely percutaneous, is feasible and can achieve the same neurological outcomes. The best surgical technique for the repair of the defect is yet to be established, and this may further improve long-term outcomes. The concerns of fetal acidosis consequent to the CO_2 used in fetoscopy seem not to occur in humans. Fetoscopy may soon become the choice for prenatal repair, restricting the role for open fetal surgery.

Conflict of interest

The author holds a patent of a trocar for fetoscopic approach.

Practice points

- Fetoscopic repair is safer for the mother and has the same neurological results for the fetus as those by the open fetal surgery.
- Two approaches are in use for fetoscopic repair: the laparotomy assisted and the percutaneous.
- Both types of fetoscopic approaches allow the patient to have vaginal deliveries, contrary to the open fetal surgery, where c-section delivery is mandatory.

Research agenda

- The best approach for the fetoscopic repair is yet to be established.
- Surgical technique for the repair of the defect needs to be standardized before conclusive comparisons are made.
- Technical improvements of entirely percutaneous approach are underway to improve the perinatal outcome; this may allow this approach to be the choice in the future.
- Fetoscopic repair training needs to be established for a safer introduction in new centers.

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