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Fetoscopic myelomeningocele closure: Is the scientific evidence enough to challenge the gold standard for prenatal surgery?

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Abstract

Since the completion of the Management of Myelomeningocele Study, maternal-fetal surgery for spina bifida has become a valid option for expecting parents. More recently, multiple groups are exploring a minimally invasive approach and recent outcomes have addressed many of the initial concerns with this approach. Based on a previously published framework, we attempt to delineate the developmental stage of the surgical techniques. Furthermore, we discuss the barriers of performing randomized controlled trials comparing two surgical interventions and suggest that data collection through registries is an alternative method to gather high-grade evidence.

Key points

What's already known about this topic?

- The use of fetoscopy for spina bifida repair is adopted by an increasing number of centers worldwide. On the other hand, its efficacy has not been established within a randomized controlled trial and thus it is still considered experimental by others.

What does this study add?

- Herein we describe a framework which could be used to determine the developmental stage of novel interventions in the field of maternal-fetal surgery. Furthermore, we discuss the difficulties of gathering high level evidence for a *fetoscopic* closure of the spinal defect in fetuses with a spina bifida.

1 | INTRODUCTION

After its publication in 2011, the Management of Myelomeningocele study (MOMS) has led to a widespread expansion of centers offering prenatal surgery for fetuses with a spina bifida.^{1,2} The benefits of

prenatal surgery are a reduction in the need for ventriculo-peritoneal (VP) shunt placement, as well as improved mental development, motor and urological outcomes.^{1,3} The downside of open maternal-fetal surgery is the high maternal morbidity and the risk of uterine rupture due to the large hysterotomy in current and subsequent

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pregnancies.⁴ In addition, any fetal intervention results in an increased risk of preterm birth and complications of prematurity.

Because of these risks many groups have explored the possibility of a fetoscopic approach already since the 1990s.⁵ One initial attempt included a maternal laparotomy but due to high maternal and fetal risks it was nearly immediately abandoned in favor of open maternal-fetal surgery.⁶ Yet, several researchers continued to explore a percutaneous fetoscopic approach.⁷⁻¹⁰ With ongoing experience more steady techniques were established, though the benefits of a minimally invasive approach were initially offset by longer surgery times, increased risk of preterm premature rupture of membranes (PPROM), preterm delivery and higher fetal and neonatal mortality.^{7,8,10-12} These discouraging results temporized many centers in adopting an endoscopic approach.

In 2017, the first clinical series of an alternative fetoscopic technique was reported, combining maternal laparotomy with a two-port fetoscopic closure (open fetoscopy).¹³ The technique is still evolving but recent results are promising, as they provided first, early evidence for a lower risk of PPRM and longer interval to delivery.¹³⁻¹⁵ In addition, albeit not evaluated in a clinical trial, the rate of VP shunting and motor outcome appeared to be in the range of what was observed in the MOMS trial.

Improving performance as well as ongoing criticisms from others triggered the idea to set up a consortium studying the outcomes of fetoscopic spina bifida closure.¹⁶ This raises the question on how exactly top-level evidence will be gathered and, for instance, whether it is justifiable not to do so in a randomized controlled trial (RCT) with head to head comparison of the investigational (fetoscopic) technique versus what is the standard of care (the open approach). Conversely, one may consider introducing the fetoscopic approach based on the available literature. In this paper, we discuss the challenges of evidence-based medicine in maternal-fetal surgery and alternatives to performing an RCT. We also propose a framework that could be used as guidance to define the developmental stage of any novel treatment, provided a wide support, a spirit of collaboration, and honest registration can be established and techniques become more consistent.

2 | CONCERNS ABOUT THE FETOSCOPIC APPROACH

The use of fetoscopy for spina bifida closure has been controversial from the moment it was introduced. The main concerns were about the safety of using CO₂ for intra-amniotic insufflation, the high intraoperative complications and fetal mortality rates, the high PPRM and preterm birth rates, the use of patches to cover the defect instead of anatomical closure and the fragmented and incomplete reporting of neurological outcomes. In the last years, many of these concerns are being addressed and more recent outcomes are encouraging (Table 1). The safety of CO₂ insufflation was questioned because initial animal experiments observed the development of a normoxic fetal acidosis, particularly at higher pressures.²⁰⁻²³

However, recent evidence has shown that this could be mitigated by reducing insufflation pressures and adjusting the humidity and temperature of the insufflated gas.²³ In addition, the effect of CO₂ in humans maybe less prominent as was recently demonstrated in a clinical case series.²⁴ Nonetheless, the latter study analyzed venous samples which may not entirely reflect the fetal pH/pCO₂ and there was a considerable delay between cessation of insufflation and sampling.²⁴ As CO₂ is highly soluble any increased values could have resolved at the time of sampling. Reassuringly, there is currently no evidence of immediate adverse effects on cerebral development based on postnatal MRI.²⁵

The initial high intraoperative complications and perinatal mortality observed with the percutaneous approach have improved in the latest experience published by the two most experienced groups in the world.^{7-9,16,26} In the most recent series, *excluding* cases from learning curves, the procedure was technically feasible in almost all cases.^{7,16} Likewise, fetal and neonatal deaths (4/131, 3%; two fetal and two neonatal deaths) were similar to what is reported for open spina bifida repair (2/91, 2%; one fetal and one neonatal death).^{7,9,16,17} In the largest series of the exteriorised-uterus fetoscopic approach, even including the learning curve, the procedure was technically feasible in 90% of cases with one fetal demise (Table 1).¹³ On the other hand, technical success is determined by the surgeon at the end of surgery, but the true benefit can only be defined by comparing outcomes.

The next big game changer is that PPRM rates are going down, in experienced hands even below the level observed following hysterotomy, and as a consequence a more advanced median gestational age at delivery. This particularly seems consistent for the fetoscopic approach with exteriorized uterus.^{13,16} The reason for this is not entirely clear. The use of heated and humidified CO₂ could partially explain this as a recent animal experiment indeed reported reduced inflammatory cell reaction in the fetal membranes compared to cold (room temperature) and dry CO₂.²³ The exteriorized uterus also enables the transuterine fixation of the membranes prior to port placement and closure at the end of the operation. A third explanation could be the difference in shear stress applied to the membranes when positioning the trocar through only one layer instead of multiple layers with a percutaneous technique.^{27,28}

These changes add to the generic advantage of all fetoscopic approaches to not mandate a caesarean section and indeed vaginal births have been reported in up to 70% of cases.¹⁶

Nevertheless, despite these promising observations there are still a number of concerns remaining. One of the main criticisms is the lack of a unified technique for the neurosurgical part of the intervention, which seems rather "eminence based." This is however not only a privilege of fetoscopy. The neurosurgical techniques are rapidly evolving making it difficult to compare outcomes not only between centers, but also within the same center. A fetoscopic repair is technically more challenging and requires specific surgical skills necessitating extensive training and a longer learning curve, recently calculated to be at least 56 cases for the percutaneous approach compared to 35 for open surgery.²⁹ This has consequences in terms

TABLE 1 Overview of procedural, pregnancy and neonatal outcomes

Cases (N)	Postnatal repair 92 ^{1,17-19}	Open fetal surgery 91 ^{1,17-19}	Percutaneous fetoscopy		Open fetoscopy 58 (40/18) ^{15c}
			Germany: 71 ⁸ (59) ^{7,9a}	Brasil: 60 ¹⁶ (80) ^b	
GA at surgery (weeks)	NA	19–25.9 ^d	21.0–29.1 ^d	24–28.9 ^d	24.9 ± 0.7/25.0 ± 0.5
Surgery times (min)	Not reported	105 ± 23.2	140–315	83–450	261 ± 58/237 ± 47
PPROM	7.6%	44%	84.3%	67%	28%/29%
Fetal demise (N)	0	1	0/71	1 (+1 TOP)/60	0/32//1/18
GA at delivery (weeks)	37.3 ± 1.1	34.0 ± 3.0	32+2	32.5 (26.9–40.7)	36.5 ± 3.5//37.6 ± 3.1
Vaginal birth	Not reported	0%	0%	22%	50%/47%
NND (N)	2/92	1/91	2/71	0/60	0/32//0/17
Dehiscence at repair site or CSF leakage	NA	13/77 (13%)	28%	10%	25%/0%
Treated for hydrocephalus	84%	44%	45%	14/30 (47%)	47%/33% ^e

Note: Data are presented as mean ± standard deviation; median (interquartile range) or absolute numbers (N), depending on what is published in the respective papers.

Abbreviations: CSF, cerebrospinal fluid; GA, gestational age; NND, neonatal death; PPROM, preterm premature rupture of membranes; TOP, termination of pregnancy; VP, ventriculo-peritoneal.

^aData are from two papers with two overlapping study populations, data depicted are for total cohort (N = 71) unless not available.

^bData from learning curve (N = 20/80) not included.

^cFourty cases between 2014 and 2017, 8 cases where surgery was not successful and outcomes for 32 cases are reported; 18 cases from 2017 onwards with triple layer repair.¹⁵

^drange.

^eonly 12/17 cases were older than 12 months.

of volume load of centers considering fetoscopic repair. This also translates into longer surgery times at a time that the fetal brain is very sensitive to external factors: during mid gestation there is extensive synaptogenesis described as brain growth spurt.^{30,31} It is unclear whether prolonged exposure to maternal anesthesia as well as CO₂ has consequences on developmental outcomes.³¹

The lack of standardization does not pertain for the surgical technique but also to the reporting of postnatal outcomes. The MOMS trial included an extensive evaluation of postnatal neurodevelopmental outcomes in a standardized blinded manner and to a contemporary cohort of infants that were operated postnatally. The majority of these infants were included in a long-term follow-up study up to 10 years of age (MOMS 2).³² There were no differences in overall adaptive behavior; however the benefit on functional mobility seems to persist to school age. as the number of infants that could independently walk community distances was twice as high (51.3% vs. 23.1%).³³ There were fewer surgeries for shunt replacement, yet the incidence of spinal cord tethering release surgery was higher in the prenatal group.³² Conversely, based on the current available evidence scattered in several publications and sometimes in absence of a control population it is difficult to determine whether the fetoscopic repair is not inferior to the open approach.^{8,34,35} The percutaneous approach is associated with a higher need of postnatal corrections for cerebrospinal fluid leakage, which maybe related to the closure technique. Its effect on the incidence of clinically relevant spinal cord tethering is yet to be determined by long-term follow-up studies. On the other hand, the

reported VP shunt rates in recent series of both fetoscopic approaches are similar to that in the prenatal surgery arm of the MOMS.¹⁶ In general, there are also promising motor outcomes, but given the diversity in the used methodology it is hard to compare actual outcomes. Like in the MOMS-trial a blinded assessment of outcomes should be performed. An option is an independent panel of experts reviewing videos, charts or direct examinations of the child at a determined age.

As a result of the above encouraging observations, fetoscopic surgery for spina bifida repair has progressed from a controversial and highly experimental treatment to an acceptable alternative that several centers consider and/or implement. This is mainly driven by the need for attenuating the obstetric consequences (uterine incision) and maternal morbidity (percutaneous approach). The current questions therefore remain on what exact technique provides optimal neuroprotection, best obstetric outcomes and reduced maternal morbidity. This prompts the next question about how the highest-quality scientific data can be obtained and when one or more experimental surgical techniques will be sufficiently documented to be considered equivalent to the current gold standard of open fetal surgery?

3 | BENEFITS OF AN RCT

Evidence-based medicine has become the cornerstone of modern healthcare. The effectiveness of any intervention is ideally

determined using the highest-quality scientific data and in this respect RCTs are considered top level. In an RCT, patient subjects are randomly assigned to one of the compared treatments, mostly one “standard” treatment and one “experimental” treatment. The process of randomization eliminates the influence of selection bias and reduces confounding factors.³⁶ This is not the case for prospective cohort series or retrospective case series providing a lower level of evidence, which is the main concern for the fetoscopic approach. In maternal-fetal therapy there have been several landmark RCTs, including the Eurofoetus trial for twin-to-twin transfusion syndrome, the Solomon laser trial, the MOMS trial and the recently completed Tracheal Occlusion To Accelerate Lung growth (TOTAL) trial.^{1,37–39} All of these have contributed to the acceptance of maternal-fetal therapy and formed the basis of ongoing collaborative consortia that strive to move this field of medicine forward. Conversely, they have taken long and often led to controversy. Also, some failed to recruit sufficient patients.⁴⁰

4 | LIMITATIONS OF AN RCT

Despite RCTs being often rated as the gold standard, this may not be applicable to every type of research.^{41,42} First, there are some concerns when it comes to RCTs evaluating surgical interventions in general. For example, all surgical RCTs are complicated by the fact that for every case there is a countless number of confounders (such as pathological findings, surgeon's expertise and surgical approach as well as shift in the management for the condition over time) which may have an effect on the standardization the investigated treatment and these are not controlled for by randomization.⁴³ A second concern is the discrepancy between the time to gather evidence from an RCT and the pace of developing novel techniques. For all the RCTs in maternal-fetal surgery mentioned above, slow recruitment made it challenging to complete enrollment of sufficient patients. The MOMS trial took nearly 10 years to complete and likewise the TOTAL trial evaluating the effect of fetoscopic tracheal occlusion for infants with a congenital diaphragmatic hernia has only recently finished recruitment after more than a decade. This could be explained partially by the rarity of these conditions but at least as much by the hesitancy of parents to undergo investigational procedures in pregnancy and physician's bias. On the other hand, most procedures will go through an experimental preclinical and clinical phase prior to the initiation of clinical trials, and this often inspires other centers to start clinical programs, who later on find it difficult to question that intervention. This so-called “back-door” phenomenon, that is, offering interventions outside of clinical trials, is common and weighs on recruitment rates. The powerful “technological imperative”—the idea that if something can be done it should be done—is an important aspect for both physician and patient and increases the urge to offer a not always thoroughly studied treatment.⁴⁴ During the MOMS trial, a moratorium was imposed by the US maternal-fetal surgical centers except for the three trial centers, but repeating a study like this to objectively assess the benefit of a fetoscopic repair seems difficult.

Fetal therapy in general often generates (social) media attention and not uncommonly this could be a driving factor.

Moreover, when for instance designing an RCT to study the benefits of a fetoscopic approach it may become difficult to identify the most relevant primary outcome and a single RCT may not answer all research questions. The main justification for a fetoscopic intervention is to improve or have at least comparable obstetric outcomes, however it should not be non-inferior concerning neurological outcomes. Therefore, two or more endpoints seem imperative.

Another reason why an RCT in maternal-fetal surgery is challenging is that it is *difficult to determine equipoise*.⁴⁵ Although there might theoretically be *equipoise*, clinical and patient *equipoise* might be difficult to achieve. The principle of *clinical equipoise* has been described by Freedman, arguing that in order to be able to enroll patients in RCTs, within the medical community there should be an overall state of uncertainty between the trial arms.⁴⁶ Yet on the other hand, every individual investigator is also influenced by personal biases, opinions and “gut-feelings” and technical skills making true clinical *equipoise* difficult to achieve.^{45–47} Moreover, often the results during the experimental stage of a novel intervention are promising and hyped, as such doctors (as well as patients) will unconsciously develop a positive bias towards one of the treatment arms. We expect that this well-known issue of “dissemination first, evidence later” is one of the most challenging factors when designing a clinical trial for a fetoscopic closure. This inadvertently influences counselling and hinders an unbiased decision to participate in an RCT.

In addition, *patient equipoise* relies on the same degree of uncertainty about the two different treatments. A source of conflict lies in the fact that the only patient is the mother, yet it is the future child who will possibly benefit from the intervention. Though the mother benefit from a less invasive procedure, the fetus (future child) may potentially benefit more from an open procedure, as this technique has proven benefit. The potential psychological benefit for the mother related to doing everything possible for her unborn child out of altruism is a very difficult item to include in a risk benefit analysis as it is almost impossible to score. As the novel procedure aims to solve a limitation of the current standard treatment this translates in a positive bias towards the investigated treatment. It is important to note that her risks and benefits not only include the benefit for the fetus, but also the implications for other family members such as future siblings.

As was underlined by Rodrigues et al., when *patient equipoise* cannot be established independently of the existence of theoretical and *clinical equipoise*, consent to randomization might not be possible and therefore RCTs become difficult to organize. The concept of *total (theoretical, clinical and patient) equipoise* is therefore described as “an overwhelmingly fragile concept” particularly for unblinded interventional studies.⁴⁶ Nevertheless, this should not be considered the only reason not to pursue randomization in maternal fetal surgery.

Another limitation is that most centers have invested in gaining expertise in one technique and thus it is challenging, maybe impossible, to find centers that can offer different

treatments in an unbiased manner. This does not only apply to studies comparing open versus fetoscopic methods, but also studies that will compare the different fetoscopic techniques (percutaneous vs. open).

Taking all together, it seems that an RCT for the comparison of the different surgical methods for prenatal spina bifida closure will be very challenging, maybe impossible for several reasons. Hence, alternative options should also be explored on how to determine when an “experimental” therapy becomes the gold standard.

5 | THE CONTINUUM OF RESEARCH

Most regulatory bodies depart from a dichotomous approach labeling treatments as either experimental or established. However, there is no clear consensus of the extent of this research phase and thus it remains unclear when available evidence is convincing enough to decide that a new technology or treatment is no longer to be labelled as “experimental”.⁴⁸ To evaluate the implementation of new technologies in the field of reproductive medicine, a conceptual framework and a scoring tool were developed.⁴⁹ We propose that with some minor adaptations, this framework can be used as a general tool for evaluating new treatments in other medical specialties, such as maternal-fetal surgical interventions (Table 2). This framework describes that the development of novel techniques ideally follows a continuum that distinguishes three categories: experimental, innovative and established treatments.⁴⁹ Experimental therapies should only be offered in a research setting, aiming at showing efficacy and safety in animals and case reports in humans (“proof of concept”), with approval of a medical research ethical committee. Innovative treatments have progressed from this initial phase and there is albeit limited evidence of efficacy and short-term safety in humans. The label “innovative treatment” entails an intermediate phase of research in a novel treatment to provide generalizable knowledge, comparable to a phase III drug research study. Obviously, this should be done with continuous oversight of regulatory bodies. The scoring tool provides a means to determine the status of a novel treatment within this continuum rating the therapy in four criteria: efficacy, safety, procedural reliability and effectiveness.⁴⁹

Within this framework, open fetal spina bifida closure is categorized as an established therapy (Figure 1). Both fetoscopic approaches would rank as innovative treatments, however based on the most recent series effectiveness could be scored as acceptable (Figure 1).^{15,16,50}

The following recommendations were suggested for interventions that fall in the innovative treatment category: (1) treatment should only be offered by expert centers; (2) there should be a commitment to closely monitor their practice conducting thorough follow-up studies with the purpose of publishing the (positive and negative) results in peer-reviewed journals; (3) patients should be adequately informed about all relevant aspects

of the procedure (including surgical expertise) and about the status of the treatment (lack of long-term outcomes should be emphasized) and (4) centers should always be prepared to stop treatment when there are signs of serious concerns based on their own studies or on published reports.⁴⁹ This also implies that all patients should also be asked for their consent for any innovative treatment and also to be contacted in the future for follow-up studies. Therefore, requiring formal approval of a medical research ethics committee is essential.

The difficulty of maternal-fetal therapy is that the status of the treatment should be balanced between the benefits and risks for the fetus and the maternal risks, and this is evidently not incorporated in the framework of Provoost et al.⁴⁹

6 | INTERNATIONAL REGISTRIES

A pragmatic alternative for evaluating the effect of surgical interventions is to generate large, prospective, cohort registries with standardized data collection for key outcomes. The data acquired within the MOMS trial were collected with a scientific rigor that is currently not present for fetoscopic interventions. There are important inconsistencies in selection criteria, operative methodology and data points differ, there is overlap between series and the postnatal outcomes are not reported uniformly.

Regardless, every center developing an innovative therapy has a moral obligation to monitor its own outcomes. Given the relative scarcity of these maternal-fetal interventions such registries need to be organized within (inter)national collaborations. Establishing collaborative networks stimulates transparency between competing centers and enabling generation of larger series assessing short- and long-term follow-up. It also offers the opportunity to unify the technique based on the collective experience of the participants, thereby accelerating the innovation phase. With this goal, a consortium of 25 North American Fetal Therapy Network centers agreed to collect data of all fetal myelomeningocele (MMC) interventions prospectively from 2012 onwards.¹⁸ In parallel, the International Fetoscopic Myelomeningocele Repair Consortium was founded in 2018 to advance knowledge on the fetoscopic technique by providing data into a common registry.¹⁶ Such international collaborations are essential and all centers performing these interventions are strongly encouraged to participate. Moreover, every effort should be made to collate registries and in order to facilitate this a minimum data set should be agreed upon covering *all* aspects of the MMC repair including maternal views and experience. In addition, a continuous comparison to contemporary cohorts of infants with postnatal closure and open prenatal surgery remains essential. But more importantly it is our responsibility as scientific community to determine the most optimal outcome measure to compare the fetoscopic versus the open approach. This consensus outcome could then be used to calculate the number of cases needed to generate the evidence to favor one of the treatments with sufficient power without performing an RCT.

TABLE 2 Scoring tool for distinguishing between treatments (modified for maternal-fetal therapy, based on Provoost et al.⁴⁹)

Criterion	Definition	Scoring
Efficacy	Proof of principle	0. No proof of principle has been demonstrated 1. ^a Proof of principle has been demonstrated <i>Efficacy' is an all-or-nothing criterion that only has one threshold</i>
Safety	Safety of the procedure, referring to: -Maternal outcomes -Fetal outcomes -Neonatal outcomes	1. Considered safe in animals 2. Reassuring "proof of concept" case reports 3. ^a Reassuring short-term data in humans (up to at least 3 months post-delivery) in peer-reviewed journals 4. ^b Reassuring mid-term data in human (up to at least 5 years post-delivery and including fertility, subsequent pregnancy outcomes and data on psychological development) in peer-reviewed journals 5. Reassuring long-term data in human (up to at least 25 years post-delivery, including data on psychological development and preferably on fertility of the operated fetus) in peer-reviewed journals
Procedure	Procedural reliability and transparency: The similarity or variability of the procedure in different centers and the potential for implementation by other centers	1. No procedure has been described yet, or the procedure varies enormously between centers 2. ^a Technical performance of the procedure is highly variable between centers 3. Technical performance of the procedure is relatively comparable between centers 4. ^b Technical performance of the procedure is highly comparable between centers 5. Throughout different centers, the procedure is considered a routine technique with common technical performance
Effectiveness	The likelihood of producing the desired outcome compared with outcome of conventional (postnatal), established therapies	1. Completely unknown, doubtful or extremely low 2. ^a Low 3. Reasonable 4. Acceptable but not as high as established therapies 5. ^b As high or higher than established therapies

^aThreshold to move from experimental to innovative treatment.

^bThreshold to move from innovative treatment to an established treatment.

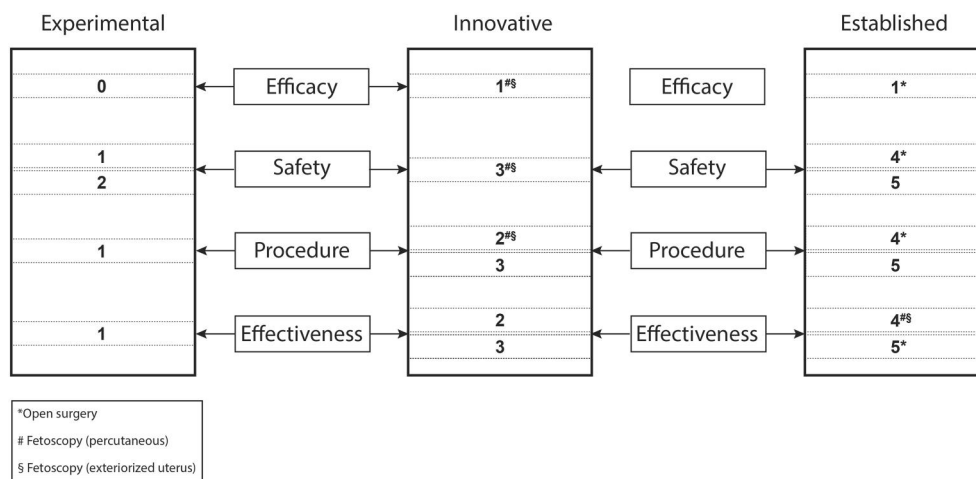


FIGURE 1 Adapted from Provoost et al.⁴⁹ Assessment tool for the transition from an experimental treatment to an innovative treatment and to an established treatment

7 | CONCLUSION

Maternal-fetal surgery has become a widespread treatment option for fetuses with a spina bifida. In pursuit of minimizing maternal risks, fetoscopic techniques are being explored. We have discussed that these inventions have progressed from an experimental to an innovative stage, albeit that the optimal fetoscopic approach has not been

determined. Nevertheless, the promising results created an expansion of centers offering such interventions, resulting in fragmentation of surgical experience and the publication of outcomes. Although an RCT is generally considered the highest level of evidence to evaluate the effects of any treatment, we foresee major difficulties organizing such a study for this indication. We propose that gathering data from high-quality international registries with standardized outcomes and

long-term follow-up could be a valuable alternative. Yet, until we are able to establish superiority of a fetoscopic approach, we cannot entirely discard the necessity of an RCT. In the absence of high-quality evidence, we emphasize the importance of careful and balanced in-depth counselling taking in consideration individual risks and benefits for every patient.

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CONFLICT OF INTEREST

No conflicts of interests to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

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