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Surgical approaches to *in-utero* spina bifida repair: a Systematic Review

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ABSTRACT

Objective. In the last decade, various surgical approaches have been proposed for the *in-utero* correction of fetal open spina bifida with variants of the classic hysterotomy technique, aimed at reducing maternal invasiveness and in an attempt to preserve the fetal benefits of the treatment. The aim of our systematic literature review is to analyze the fetal and maternal outcomes of the different surgical techniques available, describing their rationale, advantages and disadvantages.
Materials and Methods. The MEDLINE PubMed, Web of Science and EMBASE databases were searched using some keywords, alone or in different combinations.
Results. Given the absence of randomized studies and long-term outcome data, it is not possible today to argue the superiority of one technique over the other.
Conclusions. Probably both main techniques (open and fetoscopic) are destined to establish themselves with diversified indications based on the specificities of each clinical case.

INTRODUCTION

Prenatal surgery for fetal spina bifida was proven to be advantageous compared to postnatal surgical treatment in light of the improved neurological structural and functional motor outcomes in neonates and infants, as shown in Management of Myelomeningocele Study (MOMS) [1]. Doubled chances of independent ambulation was associated with higher odds of hindbrain herniation reversal and significantly reduced need for post-partum ventriculoperitoneal shunting, in patients undergoing prenatal repair [1]. Studies on pathophysiology of open spina bifida (OSB) showed the importance of avoiding the secondary damage that the spinal cord undergoes during the exposure to physical trauma and irritant chemicals contained within the amniotic fluid [2].

The MOMS was terminated earlier than planned based on efficacy of prenatal surgery on motor function and on lowering ventriculo-peritoneal shunting rates; however, improvements in bowel function, bladder function and neurocognitive outcomes were not statistically significant. Neurodevelopmental delay was not clearly associated with open spina bifida (OSB), though its relationship with the significant degree of ventriculomegaly and postnatal intervention in the form of ventriculoperitoneal shunting (VPS) is still debated [3]. Furthermore, in the prenatal surgery group the rates of chorioamniotic membrane separation (CAS), oligohydramnios, placental abruption and spontaneous membrane rupture were significantly higher compared to the postnatal repair group; gestational age at delivery was significantly lower in the prenatal repair group, as were neonatal complications linked to prematurity such as respiratory distress syndrome (RDS) [1].
The neonatal advantages of intrauterine repair along with the maternal and neonatal complications led to the development of several different surgical approaches aiming to combine neurological benefits of OSB repair with optimized obstetric and neonatal outcomes, in particular with reduction of preterm birth (PTB) [4-6].

Objective of the study

The aim of our study was to review the available literature concerning the surgical techniques for fetal OSB repair, analyzing the results, benefits and disadvantages concerning surgical outcomes, maternal-fetal and obstetric complications with particular interest to prematurity.

METHODS

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**) [7].

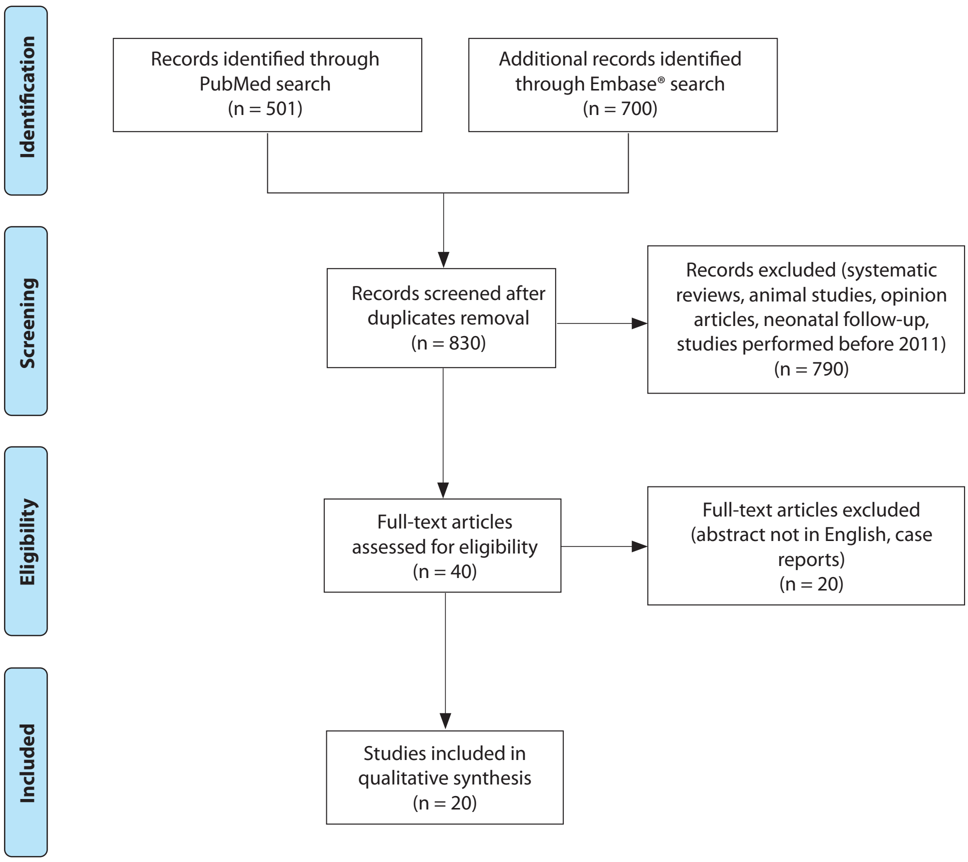

Figure 1. *PRISMA flowchart illustrating the inclusion/exclusion criteria of studies in the review.*

After screening for duplicates, 830 manuscripts were selected as relevant. We then reviewed records in light of the inclusion and exclusion criteria described above. Seven-hundred and ninety results were excluded, as they were reviews, animal studies, non-fetal studies, studies on pre-natal diagnosis of spina bifida, articles on neonatal care and post-natal management of urinary/fecal incontinence, opinion articles, neonatal follow-ups or studies performed before 2011. Of the 40 eligible articles, 20 were successively excluded as they were case reports or non-English abstracts, twenty articles were thus included in the systematic review.

Ethical standards

All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Search strategy

The MEDLINE PubMed, Web of Science and EMBASE databases were searched using the following keywords, alone or in different combinations: "myelomeningocele", "meningomyelocele", "spina bifida", "open spina bifida", "myeloschisis", and "fetus", "pregnancy", "repair", "fetal surgery", "prenatal repair".

Eligibility criteria

Studies were included in the review if they were 1) original research; 2) written in English (or abstract available in English); 3) published after 2011 (year of MOMS publication) and up to 7th of March 2021; 4) content available in full text. Studies were excluded from the review if they were 1) comments, duplicates, or not published in English; 2) not available in full text; 3) animal models or post-mortem; 4) case reports; 5) did not focus on *in-utero* open spina bifida repair.

Data items and synthesis

Two authors S.G. and G.G. independently screened the studies by title and abstract, any controversy was resolved consulting a senior author (P.I.C.). Studies that clearly violated the eligibility criteria were excluded. The following data were extracted from each study: first author's name, publication year, study design, number of patients in each group, type of surgery performed, surgery time, obstetric complications, gestational age at birth and gestational age at surgery. Since the surgical approaches to intrauterine OSB repair refers to two major techniques (open and fetoscopic approach), included studies were thus grouped and reviewed separately.

Quality assessment

Quality assessment of the included studies was achieved using the National Institute for Health and Care excellence (NICE) recommended NIH tool for the quality assessment of Case Studies Series. The grades were attributed based on questions 1–9: "good" if questions 1, 6, and 7 (principal factors) were present; "fair" if two factors were present; and "poor" or "insufficient quality" if one factor was present (**Table 1**). A global assessment (good, fair and poor) according to Agency for Healthcare Research and Quality (AHQR) standards was assigned to each study (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, last accessed March 13th, 2021).

RESULTS

A total of 20 studies fulfilled the inclusion criteria (**Figure 1**). Twelve of them dealt with open approach and eight manuscripts reported on intrauterine OSB repair using fetoscopy.

Open approach vs fetoscopy

The literature review studies for open techniques and fetoscopy are summarized in **Table 2** and **Table 3**, respectively, whereas their outcomes, including the complication percentages, are reported in **Table 4** and **Table 5**, respectively. A total of 1033 patients were examined in the 12 studies regarding open techniques, while only 127 patients were available from the 8 studies included for the fetoscopic approach. Out of the latter, 3 papers reported outcomes of the same case series [8-10], and three of the study groups used percutaneous abdominal entry [9, 11, 12].

The weighted mean gestational age at surgery for open technique was 24.6 weeks (range, 23.2-25.4 weeks) but was not reported by four studies [1, 13-15]. For fetoscopy the weighted mean gestational age at surgery was greater: 25.8 weeks (range, 23.7-28.2 weeks). The weighted mean gestational age at delivery for open technique studies (not reported in two studies) [14, 16] was 34.2 weeks (range, 31.7-35.1 weeks). This appeared to be at a later gestational age compared to fetoscopy studies (weighted mean 33.4 weeks; range, 32.4-38.1 weeks).

Among the complications reported, one of the most relevant was preterm birth (PTB); in the open approach, Zaretsky *et al.* [17] reported 83% of patients delivering at or before 34 weeks, while the rate of this complication among all considered open approach studies ranged from 20% to 83%. The percentages of PTB < 34 weeks in the fetosco-

Table 1. *Quality Assessment of the Included Studies.*

	1. Was the study question or objective clearly stated?	2. Was the study population clearly and fully described, including a case definition?	3. Were the cases consecutive?	4. Were the subjects comparable?	5. Was the intervention clearly described?	6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	7. Was the length of follow-up adequate?	8. Were the statistical methods well-described?	9. Were the results well-described?	**GRADE AHRQ standards**
Adzick *et al.*, 2011 [1]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	**Good**
Moldenhauer *et al.*, 2015 [34]	Yes	Yes	NA	NA	Yes	Yes	No	Yes	Yes	**Good**
Zamlynski *et al.*, 2014 [16]	Yes	Yes	CD	Yes	Yes	Yes	CD	CD	Yes	**Fair**
Friszer *et al.*, 2016 [35] (article in French)	No	Yes	No	Yes	Yes	No	NA	NA	Yes	**Poor**
Bennett *et al.*, 2014 [13]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	**Good**
Zaretsky *et al.*, 2018 [17]	Yes	Yes	CD	Yes	Yes	Yes	No	Yes	Yes	**Fair**
Moron *et al.* 2018 [36]	Yes	Yes	Yes	NA	Yes	Yes	No	Yes	Yes	**Fair**
Peralta *et al.*, 2020 [19]	Yes	Yes	Yes	NA	Yes	Yes	No	Yes	Yes	**Good**
Sepulveda *et al.*, 2020 [15, 22]	Yes	Yes	CD	NA	NA	Yes	No	Yes	Yes	**Good**
Pruthi *et al.* 2020 [15]	Yes	Yes	Yes	NA	Yes	Yes	No	Yes	Yes	**Fair**
Cruz Martinez *et al.*, 2020 [23]	Yes	Yes	CD	NA	Yes	Yes	No	Yes	Yes	**Fair**
Moehrelen *et al.*, 2021 [14]	Yes	Yes	NA	NA	Yes	Yes	No	Yes	Yes	**fair**
Kohl *et al.*, 2014 [9]; Degenhardt *et al.*, 2014 [8]; Graf *et al.*, 2016 [10]	Yes	Yes	CD	Yes	Yes	Yes	No	Yes	Yes	**Good**
Belfort *et al.*, 2017[18]	Yes	Yes	CD	Yes	Yes	Yes	Yes	NA	Yes	**Good**
Giné *et al.*, 2018 [37]	Yes	Yes	CD	NA	Yes	Yes	No	NA	Yes	**Fair**
Belfort *et al.*, 2020 [20]	Yes	Yes	CD	CD	NA	Yes	Yes	Yes	Yes	**Good**
Lapo Pedreira *et al.*, 2018 [12]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	**Good**
Carrabba *et al.*, 2019 [11]	Yes	Yes	CD	NA	Yes	Yes	No	Yes	Yes	**good**

CD: cannot determine; NA: not applicable; NR: not reported.

py groups ranged from 0% (in the 10 patients from the "standardized technique" group described by Belfort *et al*., in 2017) [18] to 51% [9].

As for preterm premature rupture of membranes (pPROM), the reported rate in the "open technique" group ranged from 15.0% to 53.8% (**Table 4**), with a weighted mean percentage of 28.7%; in fetoscopy studies, the weighted mean percentage was higher at 59.1% (range, from 10.0% to 84.4%) (**Table 5**). Furthermore, 3 out of the 9 fetoscopic case series reported a pPROM incidence of above 80% [9, 11, 12]. When observing the other outcomes, it should be noted that in open repair the rate of post-partum neonatal dehiscence was lower (as low as 0% in the study published by Peralta *et al*. in 2020 [19], with a maximum of 13% in the earlier reports) compared to fetoscopy (with studies reporting a peak at 31% in patients treated with the single layer technique described by Belfort *et al*. in 2020) [20]. Additionally, the rate of postnatal VPS/endoscopic third ventriculostomy ranged from 0% to 41% in open studies, while it was above 50% in 3 of the fetoscopy patient groups (range, from 20% to 75%) (**Table 5**) [11, 12, 18].

Postnatal repair of the fetal dehiscence occurred in less than 15% of neonates who had undergone open repair in all studies under revision (range, from 0% to 13%) while 5 out of the 9 fetoscopy case series reported the need for this intervention in more than 15% of cases (range, from 0% to 31%).

DISCUSSION

Summary of main results

The two main approaches (open and fetoscopic) present several different surgical variants according to the proposal of different groups. The technique described in the first trial involving open repair of OSB ("MOMS trial") consisted of uterine exteriorization and examination through ultrasound (US); placental and fetal location then were determined, and the fetus was manually mobilized so that the MMC/myeloschisis could be approached via a hysterotomy without damaging the placenta. A stapler was then

Table 2. *Open techniques for intrauterine myelomeningocele repair.*

Author, year	Patient no	Mean GA at surgery (weeks ± SD)	Mean GA at delivery (weeks ± SD)	Technical details	Surgery duration (mins ± SD)
Adzick *et al.*, 2011 [1]	78	23.6 ± 1.4	34.1 ± 3.1	6-8 cm hysterotomy	105 ± 21.8
Moldenhauer *et al.* 2015 [34]	100	23.4 ± NR	34.3 ± NR	6-8 cm hysterotomy; MOMS protocol.	78.5 ± NR
Zamlynski *et al.*, 2014 [16]	46	24.7 ± 7.9	NR; 34.1% delivered < 30 gw	6-8 cm hysterotomy	NR
Friszer *et al.*, 2016 (article in French) [35]	3	23.6 ± 2.1	34.5 ± 1.4	5-6 cm hysterotomy	130 ± NR
Bennett *et al.*, 2014 [13]	43	NR	34.4 ± 6.6	6 cm hysterotomy (uterine entry using electrocautery as opposed to a trocar)	NR
Zaretsky *et al.*, 2018 [17]	43	23.2 ± 1.2	31.7 ± 3.8	6-8 cm hysterotomy. Uterine closure: interrupted full thickness suture + running suture to realign myometrial edges + third imbricating layer serosal to serosal apposition.	NR
Moron *et al.* 2018 [36]	237	25.2 ± 0.4	33.6 ± 2.4	Hysterotomy (4-6 cm). Allis clamps and stitches to avoid the use of surgical stapler,	119 ± 7.6
Peralta *et al.*, 2020 [19]	190	24.6 (median) ± 2.1	NR (median 35.3)	2.5 – 3.5 cm Mini-hysterotomy; Running suture to secure membranes to the myometrium; Use of Ankeney retractor; Partial uterine exteriorization; uterine wall incision at a distance of 2 cm from the placental edge. 2-3 layer hysterorraphy.	200 ± NR
Sepulveda *et al.*, 2020 [22]	58	24.8 ± 0.9	33.3 ± 3.6	3-4 cm Hysterotomy, between 20+0 and 27+0 gw. Membrane anchoring to myometrium with polyglactin. Use of collagen patch in 9 cases, skin incisions in 1 case.	NR
Pruthi *et al.* 2020 [15]	27	24.4 ± 2.0	34.9 ± 3.0	6-8 cm hysterotomy (MOMS technique). Bilateral advancement flaps (n = 4) and acellular dermal matrix patch (n=5) were used in some cases	NR
Cruz Martinez at al.,2020 [23]	60 (13 classic open technique, 47 open microneurosurgery technique)	Classic: 25.4 ± 1. microneurosurgery 25.1 ± 0.82	Classic: 32.7 ± 4.1. microneurosurgery 35.1 ± 3.0	Microneurosurgery: 20 to 15 mm uterine incision. The fetal back is fixed to the hysterotomy with 2 monofilamento 4-0 stitches. In cases of myeloschisis a bilayer collagen implant was used.	Classic 120.6 ± 25.4 Microneurosurgery 107.3 ± 30.3
Moehrlen *et al.*, 2021 [14]	148	NR	35.23 (median) (range 25.23 to 36.86)	6-8 cm hysterotomy (MOMS technique); 2017 paper (38) reports the possibility of using distally pedicled random pattern transposition flaps if the skin defect is extended.	NR

Gestational age at surgery, at delivery and surgery duration values are reported as mean ± standard deviation unless differently stated. GA: gestational age; PTB: preterm birth; pPROM: preterm premature rupture of membranes; VPS: ventriculo-peritoneal shunting; ETV: endoscopic third ventriculostomy; CSF: cerebrospinal fluid; SD: standard deviation.

used to create a 6-8 cm uterine incision and the MMC was exposed. The neurosurgical approach consisted of sharp dissection of the neural placode from the surrounding tissue, closure of the dura with a running suture and skin closure using a fine running monofilament suture. The uterus was then closed with a first layer encompassing the absorbable staples and the uterine membranes (after amniotic fluid replacement with ringer's lactate and antibiotic) and a second imbricating layer of suture. This technique was then modified by other surgeons to minimize invasiveness and improve fetal neonatal outcomes (**Table 2**). Of note, some authors avoid the use of surgical staplers and prefer to suture the membranes to the inner layer of the myometrium before the beginning of the MMC/myeloschisis closure [21]. This intervention is likely to be the reason the incidence of pPROM is lower (< 30%) in more recent reports on open OSB repair, as compared to fetoscopic approaches in which generally suturing of membranes is not described (**Table 4** and **Table 5**) [15, 19, 22, 23].

Given the advantages of a lower maternal invasiveness and the possibility of a vaginal delivery thereafter, fetoscopy has been extensively studied and modified too. Uterine entry during fetoscopic repair is through smaller uterine incisions (using a range of 2 to 4 entry ports), thereby reducing the risk of uterine dehiscence. However, entry ports are numerous and membranes are not sutured after trocar removal, leading to an increase in the rate of pPROM (**Table 5**) [24]. Furthermore, in light of the problems of operating fetoscopically in fluid, insufflation of the amniotic cavity with carbon dioxide is implemented to perform fetoscopy (PACI, "partial amniotic carbon dioxide insufflation"). There have been reports of complications such as fetal acidosis, trocar dislodgement, CO_2 leakage in maternal abdomen and damage to amnio-chorial membranes with this method [18, 25-29]. Minimal access percutaneous fetoscopic closure also requires favorable fetal posturing and placental position, to the point of needing to postpone the procedure until a more auspicious fetal position is obtained in some instances. Additionally, in obese patients and anterior placentae having a good transcutaneous US guidance can be challenging. The defect is seldom closed with single layer or multilayer technique used by pediatric neurosurgeons, but the use of patches is introduced to work around the technical difficulties of a fetoscopic multilayer closure, and relaxing skin incisions are often performed if a satisfying dissection of the neural placode is not achieved [29]. This leads to the undesired high rates of neonatal reintervention for OSB repair (**Table 5**). Among the various fetoscopic techniques, it should be highlighted that in fetoscopic repair via maternal laparotomy the incidence of preterm birth is not as high as it is in percutaneous fetoscopic repair.

Few of the available studies present enough statistical power for being conclusive in defining rates of maternal complications as well as pregnancy and neurological outcomes. Overall, we recognize that fetoscopic approaches are less invasive for the mother, on average show greater gestational age at intervention, an increased risk of prematurity but a higher proportion of less effective treatment for the fetus (higher rates of postnatal ventricular-peritoneal shunting) as compared to open surgical approaches. However, given the heterogeneity of patients and disease characteristics, as well as the lack of long-term outcome data in the study groups, these apparent differences cannot result in a definitive evidence of superiority of one procedure against the other.

Interpretation

In light of the various surgical techniques described in medical literature, we believe that a critical point for developing research in the field of surgical treatment of fetal OSB is standardizing patient counseling according to different protocols and expected outcomes in order to deliver objective, evidence-based and non-directive counselling enabling an informed choice for eligible patients in Italy. This is unfortunately not the case yet, and we advocate future research on this topic in order to allow all patients the chance to be fully informed about treatment options following the diagnosis of fetal OSB. An interesting new concept stems from the knowledge that fetuses operated on earlier in pregnancy are less prone to receiving post-natal ventriculoperitoneal shunts [19].

At present, it is evident that the fetoscopic approach is promising as it reduces some of the complications related to the "larger" uterine incision needed to achieve a satisfying MMC correction in open surgery and could allow for a successive vaginal delivery; in fact, in our literature review, none of the studies on fetoscopic approach reported any uterine ruptures, although as can be seen in **Table 4**, this was an extremely rare occurrence in open repair too. Furthermore, the mean weighted gestational age at delivery was higher in patients undergoing the open approach compared to those undergoing fetoscopy.

Table 3. *Fetoscopic techniques for intrauterine myelomeningocele repair.*

Author, year	Patient no	Mean GA at surgery (weeks ± SD)	Mean GA at delivery (weeks ± SD)	Technical details	Surgery duration (mins ± SD)
Kohl *et al.*, 2014 [9]; Degenhardt *et al.*, 2014 [8]; Graf *et al.*, 2016 [10]	51	23.7 ± NR	33.0 ± NR	Percutaneous Amniotic fluid removal and use of PACI Three (n=49) or four (n=2) 5 mm fetoscopic ports inserted at a minimum of 3 cm from the placental edge Fetoscopic placode dissection, collagen patch	NR (successful cases reported between 140 and 315 minutes)
Belfort *et al.*, 2017 [18]	22 (12 iterative, 10 standardized)	25.0 ± NR (fetoscopic. n = 12) 25.4 ± NR (iterative)	38.1 ± NR (fetoscopic) 35.9 ± (iterative)	Laparotomic Amniotic fluid removal and use of PACI Two uterine ports Single layer MMC closure Use of relaxing lateral skin incisions if required	Standardized fetoscopic: 246 ± NR Iterative: 267 ± NR
Giné *et al.*, 2018 [37]	5	24.4 ± NR	34.1 ± NR	Laparotomic Two-layer MMC closure (myofascial and cutaneous)	169.0 ± 17.5
Belfort *et al.*, 2020 [20]	32 (single layer closure) 18 (three-layer closure)	25.0 ± 0.7 (single layer closure) 25.0 ± 0.5 (three-layer closure)	36.5 ± 3.5 (single layer closure) 37.6 ± 3.0 (three-layer closure)	Laparotomic, uterine exteriorization. The 3-layer MMC closure: bovine collagen patch, myofascial layer, cutaneous layer.	Single layer: 132.1 ± 50.4 3-layer closure: 166.4 ± 40.7
Lapa Pedreira *et al.*, 2018 [12]	45 (including patients from CECAM trial; 32 single, 13 double patch))	Single patch: 26.7 ± 1.03 Double patch: 26.9 ± 1.04	Single patch: 32.4 ± 2.5 Double patch: 33.7 ± 2.6	Percutaneous 32 patients underwent a single biocellulose patch positioning 13 patients underwent double patch positioning (biocellulose + silicone and dermal matrix)	Single patch: 193 ± NR Double patch: NR
Carrabba *et al.*, 2019 [11]	5	28.2 ± 0.4	33.9 ± 3.6	Percutanous Seldinger technique. Four patients were treated with a biocellulose patch; 1 patient with the 2-layer closure technique.	204 ± 50.8

Gestational age at surgery, gestational age at delivery and surgery time values are reported as mean ± standard deviation. GA: gestational age; PTB: preterm birth; pPROM: preterm premature rupture of membranes; VPS: ventriculo-peritoneal shunting; ETV: endoscopic third ventriculostomy; CSF: cerebrospinal fluid; CAS: chorioamniotic membrane separation; SD: standard deviation.

However, similarly to what is reported in current medical literature, the rates of premature rupture of membranes, dehiscence and leakage from the MMC repair site are lower in open repair with respect to fetoscopy [26, 30]. In fact, the 53.8% of pPROM in the "classic" open technique reported by Cruz-Martinez in 2020 was successively significantly improved by the introduction of the microneurosurgical technique reported in the same paper. Moreover, the need for postnatal revision of the repair site is higher after fetoscopic OSB correction and makes this option less appealing to pregnant patients choosing to undergo surgery for the well-being of their unborn child (**Table 4** and **Table 5**) [11].

Personal views and perspectives

Since the year 2018, surgical correction with the mini-hysterotomy initially described by Botelho *et al.* [21] was implemented at our center in the San Raffaele Hospital, Milan, Italy. The procedure was successfully implemented after an extensive onsite training and continued with tele mentoring during the pandemic [31] leading to the surgical independence of our team with objectively excellent results aligned with the current literature [32]. We are currently following the infants up to assess their functional motor, visceral and neurocognitive statuses. It should be emphasized that prenatal early diagnosis, referral to an adequate tertiary fetal medicine center and extensive patient counseling are fundamental elements for a successful *in-utero* OSB correction. Given the fact that long-term outcomes are lacking and that an earlier gestational age at intervention was recently shown to be related to improved postnatal outcome after fetal surgery [19] it is now mandatory to implement first trimester screening for spina bifida which was shown to be effective and safe and easily implemented in screening protocols [33]. Earlier diagnoses would provide adequate time for ap-

propriate prenatal investigations and counselling to patients with affected fetuses with objective, standardized and non-directive methodology. This will lead to earlier interventions before 20-22 weeks most likely with open approaches. On the other side, cases with later diagnoses and interventions (after 24-26 weeks) or maternal morbidity may benefit more of less invasive fetoscopic approaches.
Thus, in the future it is likely that different patients may require individualized, diverse surgical approaches according to their maternal-fetal characteristics, chronic morbidities, anatomy of the spinal defect, gestational age at diagnosis and at intervention. This speculation needs to be tested for confirmation but is highly plausible and well aligned with current concepts of personalized-precision medicine and surgery.

Strengths and limitations

This study has the strength of summarizing the available literature enabling assessment of pros and cons of each techniques favoring knowledge on this important topic.

Table 4. *Reported risks of complications in "open technique" studies.*

Author, year	pPROM rate	PTB (< 34 wks)	CAS	Chorioamniositis	Abruptio placentae	Uterine scar dehiscence	Uterine rupture	Fetal repair dehiscence	Perinatal mortality	Neonatal VPN/ETS shunt positioning
Adzick *et al*., 2011	46	46	26	3	6	10	NR	13	3	40
Moldenhauer *et al*. 2015	32	46	23	4	2	8	NR	3.6	6	2.4
Zamlynski *et al*, 2014	52.2	59.1	17.3	4.3	4.3	10.8	2.2		4.3	27.8
Friszer *et al*., 2016 (article in French)	33.3	33.3	NR	NR	NR	0	NR	NR	0	0
Bennett *et al*., 2014	22	32.6	0	NR	2.3	7	0	7	2.3	41
Zaretsky *et al.,* 2018	NR	83	41	NR	NR	2.3	0	NR	NR	NR
Moron *et al.,* 2018	26.7	52.1	20.8	3	0.8	3.8	NR	2.5	2.1	NR
Peralta *et al*., 2020	28.3	28.4	NR	0	5.2	3.5	NR	0	5.3	13.9
Sepulveda *et al*., 2020	25.4	40	7	1.7	0	1.8	NR	7.2	9	25
Pruthi *et al.,* 2020	15	27	NR	NR	NR	NR	NR	NR	12	36
Cruz Martinez *et al*., 2020 (classic)	53.8	61.5	30.8	7.7	7.7	0	NR	NR	23.1	20
Cruz Martinez e*t al*., 2020 (microneurosurgery)	19	21.4	21.4	4.8	0	0	NR	NR	4.8	7.2
Moehrlen *et al*., 2021	NR	20	15	1.4	0.7	NR	0.7	0.7	0.7	23

All results are given in percentages (%). PTB: preterm birth; pPROM: preterm premature rupture of membranes; VPS: ventriculo-peritoneal shunting; ETV: endoscopic third ventriculostomy; CSF: cerebrospinal fluid; CAS: chorioamniotic membrane separation.

Table 5. *Reported risks of complications in "fetoscopy" studies.*

Author, year	pPROM rate	PTB (< 34 wks)	CAS	Chorioamniositis	Abruptio placentae	Uterine scar dehiscence	Uterine rupture	Fetal dehiscence repair	Perinatal mortality	Neonatal VPS/ETV shunt positioning
Kohl *et al*., 2014; Degenhardt *et al*., 2014; Graf *et al*., 2016	84.3	51	4	4	0	0	NR	21	4	45.3
Belfort *et al*., 2017 (standard)	33	0	20	0	10	0	NR	20	0	30
Belfort *et al*., 2017 (iterative)	10	50	45	0	8	0	NR	0	0	75
Giné *et al*., 2018	60	NR	NR	20	0	0	NR	0	0	20
Belfort *et al*., 2020 (single)	28	25	41	0	6	0	NR	31	0	47
Belfort *et al*., 2020 (three-layer)	29	24	39	0	0	0	NR	6	6	33
Lapo Pedreira *et al*., 2018 (single)	84,4	NR	NR	NR	NR	NR	NR	16	6	43
Lapo Pedreira *et al*., 2018 (double)	69	NR	NR	NR	NR	NR	NR	15	0	54
Carrabba *et al*., 2019	80	40	NR	20	0	0	NR	NR	20	60

All results are given in percentages (%). PTB: preterm birth; pPROM: preterm premature rupture of membranes; VPS: ventriculo-peritoneal shunting; ETV: endoscopic third ventriculostomy; CSF: cerebrospinal fluid; CAS: chorioamniotic membrane separation.

The limits of this study are that it compares outcomes from different reports with diverse methodologies and probably different severity of the underlying fetal malformation. Moreover, it should be highlighted that our results are skewed by the fact we had a larger group of patients for the "open technique" group compared to the "fetoscopic" one. These limitations may all affect proportion of the described outcomes.

CONCLUSIONS

Based upon available literature and knowledge we cannot establish which technique presents the best maternal-fetal results for OSB *in-utero* correction. At present, fetoscopic techniques show minimization of maternal complications and open techniques have the best fetal and neonatal outcomes. However, given the advantages that antenatal MMC repair confers to neonatal outcomes, it is dutiful to continue investigating the best approach for this intervention. It will also be interesting to perform analyses once the long term post-natal cognitive and functional outcomes are examined. In light of the current available literature and our personal experience, we feel that in our setting developing the mini-hysterotomy technique may be the most promising and appropriate route. In fact, at present greater neurological benefits achieved with open fetal surgery (which are the primary goal of prenatal treatment) are still overtaking maternal benefits of fetoscopic techniques. Randomized controlled trials involving standardized techniques are required to provide scientific evidence to our impression.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

S.G., P.I.C., P.M., M.C., F.C.A.P: design, search strategy. S.G., G.G.: independent screening of studies by title and abstract, independent assessment of study eligibility by full-text review, selection of studies, independent data extraction. P.I.C.: supervision. S.G., L.A., G.G.: screening of extracted data. P.M, S.A., F.L., P.I.C., F.C.A.P.: Writing – review & editing.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

N/A.

Data sharing

Data are available under reasonable request to the corresponding author.

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