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Fetal Surgery for Myelomeningocele: A Systematic Review and Meta-Analysis of Outcomes in Fetoscopic versus Open Repair

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Keywords
Myelomeningocele · Spina bifida · Prenatal treatment · Fetal surgery · Fetoscopy

Abstract
Background/Objectives: The Management of Myelomeningocele (MMC) Study (MOMS) showed that prenatal repair of MMC resulted in improved neurological outcomes but was associated with high rates of obstetrical complications. This study compares outcomes of open and fetoscopic MMC repair. ***Data Sources:*** PubMed and Embase studies reporting outcomes of fetal MMC repair published since the completion of the MOMS. ***Results:*** We analyzed 11 studies and found no difference in mortality or the rate of shunt placement for hydrocephalus. Percutaneous fetoscopic repair was associated with higher rates of premature rupture of membranes (91 vs. 36%, $p < 0.01$) and preterm birth (96 vs. 81%, $p = 0.04$) compared to open repair, whereas fetoscopic repair via maternal laparotomy reduced preterm birth. The rate of dehiscence and leakage from the MMC repair site was higher after both types of fetoscopic surgery (30 vs. 7%, $p < 0.01$), while the rate of uterine dehiscence was higher after open repair (11 vs. 0%, $p < 0.01$). ***Discussion:*** Fetoscopic repair is a promising alternative to open fetal MMC repair with a lower risk of uterine dehiscence; however, fetoscopic techniques should be optimized to overcome the high rate of dehiscence and leakage at the MMC repair site. A fetoscopic approach via maternal laparotomy reduces the risk of preterm birth.

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Introduction

Myelomeningocele (MMC) is the most severe form of spina bifida characterized by protrusion of the spinal cord and the meninges through a defect in the vertebral column and a spectrum of clinical manifestations including hindbrain herniation, hydrocephalus, sensory and motor neurological deficits, bowel dysfunction, and urinary dysfunction [1, 2]. The estimated birth prevalence of spina bifida in the USA is 3.5 per 10,000 live births [3].

According to the "two-hit hypothesis," exposure of the neural tissues to amniotic fluid and ongoing intrauterine trauma lead to secondary damage throughout gestation [1, 4–6]. With the advent of fetal surgery, in utero repair of MMC was introduced as an attempt to limit further intrauterine damage to the spinal cord [1]. In 2011, a randomized controlled trial known as the Management of Myelomeningocele Study (MOMS) was conducted at three maternal-fetal centers in the USA, investigating outcomes of prenatal versus postnatal repair of MMC [7].

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A standardized operative approach was adopted that included a maternal laparotomy, a stapled hysterotomy, dissection of the neural placode from surrounding tissues, primary closure of the dura, and primary closure of the fetal skin [7]. The investigators found that prenatal repair of MMC reversed or corrected hindbrain herniation and reduced the need for ventriculoperitoneal shunt (VPS) placement at 12 months of age (40 vs. 82%). Prenatal repair also improved the composite score for mental development and motor function at 30 months of age. Based on the efficacy of prenatal repair in these initial results, the trial was terminated early, given the clear benefit that prenatal repair had over postnatal repair. Open fetal repair of MMC with watertight closure of the dura and closure of the overlying skin thus became the gold standard for prenatal repair of MMC.

While prenatal repair reduced the morbidity of MMC, as with any fetal intervention, it was also associated with higher rates of obstetrical complications including oligohydramnios, chorioamniotic (CA) membrane separation, placental abruption, premature rupture of membranes (PROM), preterm delivery, and uterine scar dehiscence compared to postnatal interventions [7–9].

To standardize the technique during the MOMS, minimally invasive or fetoscopic repair of MMC was temporarily halted in the USA; however, the technique continued to develop in Germany and Brazil. Proponents of fetoscopic MMC repair argue that this minimally invasive approach reduces the rate of obstetrical complications associated with open fetal MMC repair [10–13]. However, critics have argued that the high rates of membrane rupture and premature birth – combined with the inability to reliably perform a watertight closure of the MMC defect, thus necessitating postnatal revision of the repair – challenge the notion that fetoscopic MMC repair is associated with less morbidity than open fetal repair [14–18].

The purpose of this study is to systematically review the post-MOMS literature, including large and small cohorts, to investigate the obstetrical, neonatal, and 12-month neurological outcomes of patients with MMC who underwent fetoscopic versus open in utero repair.

Data Sources

Eligibility Criteria

All studies reporting outcomes of prenatal repair of MMC and published following the publication of the MOMS results by Adzick et al. [7] in 2011 were eligible. Only studies published after January 1, 2011, in French or English with available full texts were considered. Retrospective case series, retrospective case-control studies, and prospective observational studies were included. There were no randomized controlled studies comparing fetoscopic versus open fetal MMC repair. No restrictions were made based on length of follow-up.

Information Sources

A systematic review was performed in PubMed and Embase of studies published since January 1, 2011. The date of last search was August 13, 2016. A study on fetoscopic MMC repair published in 2017 was added.

Search Strategy

The following keywords were used: myelomeningocele, meningomyelocele, spina bifida, spinal dysraphism, repair, closure, prenatal repair, prenatal care, fetal surgery, and in utero. Table 1 summarizes the search strategy in both PubMed and Embase.

Study Selection

Titles and abstracts were screened, and studies on prenatal repair of MMC were selected as relevant. Studies focusing only on the postnatal repair or medical management of MMC, as well as all basic and translational science studies, were not considered relevant for the meta-analysis.

The full texts of the relevant studies were obtained and reviewed. Studies that reported fetal, obstetrical, or postnatal outcomes after in utero repair of MMC were selected. The selected studies were further reviewed for duplication of the study population. The most relevant clinical studies were then included in the meta-analysis.

Data Extraction

A list of fields to be populated was established and data from each selected study were extracted. Duplications were eliminated based on the names of authors, institutions, and study periods. Only data clearly reported by the authors were recorded and no assumptions were made. Two authors, S.K.K. and G.W.J., reviewed and analyzed the data.

The data fields included year of publication, first author, senior author, country where fetal MMC repairs were performed, study period, type of study, length of follow-up, type of fetal MMC repair, number of cases, mean gestational age (GA) at repair, status of completion of the intended operation, rate of PROM, CA membrane separation, placental abruption, uterine dehiscence, mean GA at delivery, delivery <30 weeks' GA, delivery

Table 1. Search strategy in PubMed and Embase

PubMed	Embase
Search parameters: 01/01/2011 to 08/13/2016; published articles; French/English	Search parameters: 01/01/2011 to 08/13/2016; published articles; French/English
– Initial search: "myelomeningocele" *Query translation:* "meningomyelocele" OR "myelomeningocele" **– 2nd search: "spina bifida"** *Query translation:* "spinal dysraphism" OR "spina bifida" **– 3rd search: "repair"** *Query translation:* "wound healing" OR "repair" **– 4th search: "prenatal repair"** *Query translation:* "prenatal care" OR ("prenatal" AND "care") OR ("prenatal" AND ["wound healing" OR "repair"]) – **5th search: "fetal surgery"** *Query translation:* (["fetus" OR "fetal"] AND ["surgery" OR "surgical procedures, operative" OR "general surgery"]) **– 6th search: "in utero"** *Query translation:* "uterus" OR "utero" **– 7th search: "closure"** *Query translation:* closure	Search #1: myelomeningocele (use meningomyelocele) Search #2: spina bifida (use spinal dysraphism) Search #3: spinal dysraphism Search #4: meningomyelocele Search #5: search #1 OR search #2 OR search #3 OR search #4 → 2,062 results Search #6: prenatal care Search #7: fetal Search #8: utero Search #9: search #6 OR search #7 OR search #8 → 51,029 results Search #10: repair Search #11: surgery Search #12: closure Search #13: search #10 OR search #11 OR search #12 → 705,151 results
Combined searches 1st search: "myelomeningocele" or "spina bifida" → 2,080 results 2nd search: 1st search AND "repair" → 226 3rd search: 1st search AND "prenatal repair" → 62 4th search: 1st search AND "fetal surgery" → 184 5th search: 1st search AND "in utero" → 84 6th search: 1st search AND "closure" → 162 7th search: 2nd OR 3rd OR 4th OR 5th OR 6th search → 438 studies, **176 selected as relevant**	Search #14: search #5 AND search #9 AND search #13 → 157 studies, **106 selected as relevant**

≥35 weeks' GA, term delivery (≥37 weeks' GA), mean birth weight, fetal loss, postnatal death, overall mortality at 12 months, shunt placement for hydrocephalus at 12 months, postnatal dehiscence or leakage at the MMC repair site, motor response relative to the anatomic level of the lesion, and complete reversal of hindbrain herniation. Data not clearly reported by the authors were recorded as not specified.

Risk of Bias in Individual Studies

The studies selected for inclusion in the meta-analysis were retrospective or nonrandomized prospective. We used the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0, to assess the quality of these studies and the risk of bias [19].

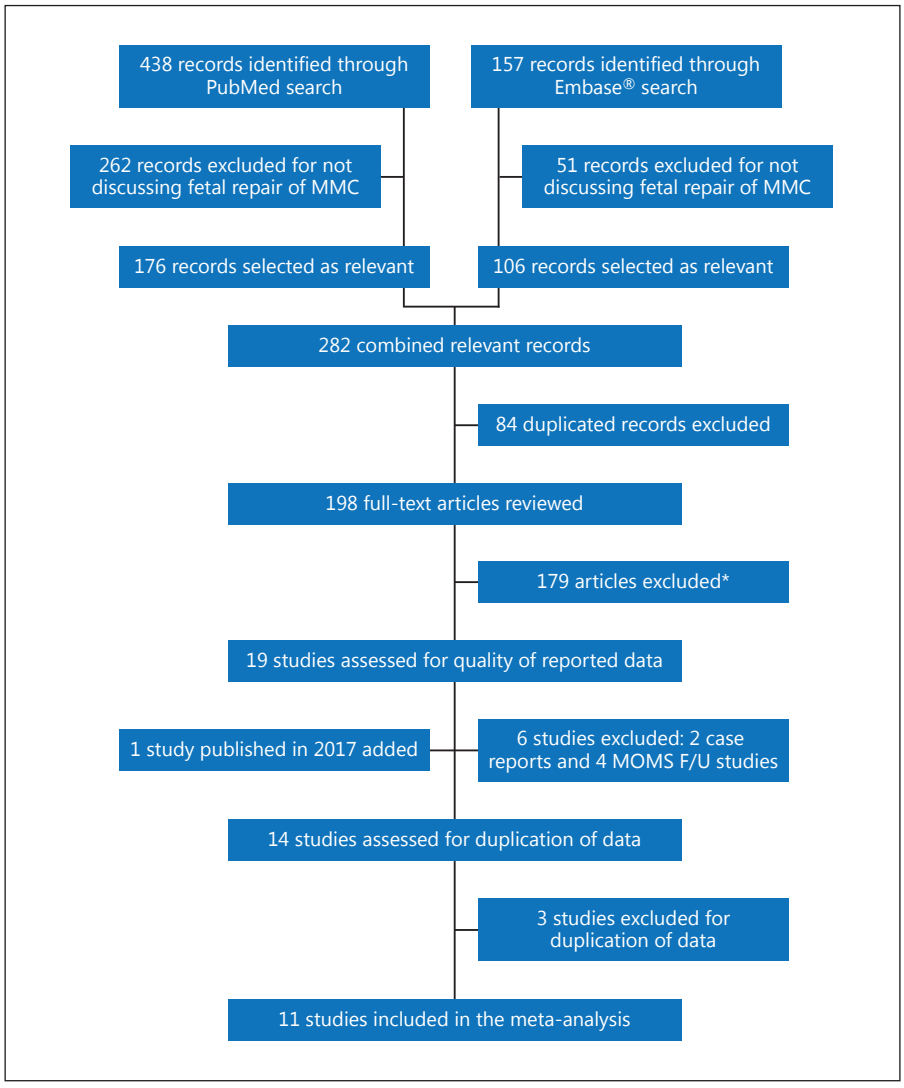
Summary Measures

The effect size used in the meta-analysis was the proportion of outcomes in each study, which was reported as the number of outcomes per sample size. The effect size was transformed using the arcsine square root of the proportion, which was weighted across studies based on the sample size. The weight was the inverse of the variance of the transformed proportion.

A weighted proportion of each outcome was obtained for all studies on fetoscopic MMC repair and for all open in utero repair of MMC. The precision of the weighted proportion was evaluated by the 95% confidence interval (CI). A 95% CI was computed for the weighted average of the transformed proportions, then back-transformed to obtain the weighted proportion and its CI. All analyses were completed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Synthesis of Results

The homogeneity of the studies was analyzed by calculating Q, which was interpreted using the χ^2 test, with a p value ≤0.05 rejecting the null hypothesis of homogeneity.



Color version available online

Fig. 1. Flowchart of study selection through different phases of the systematic review. The 11 studies included in the meta-analysis had information about the surgical approach and on obstetrical and postnatal outcomes. MMC, myelomeningocele; F/U, follow-up; MOMS, Management of Myelomeningocele Study. * The excluded articles were either opinion articles, comments to the editor, or focused instead on the prenatal diagnosis, summary, and review of MMC and its treatment, summary of perioperative care, management of urological morbidity, ethical issues surrounding fetal surgery, epidemiology, and translational research.

The statistical analysis of heterogeneity was completed by calculating I^2, with the following interpretation: 0–40%, "may not be important"; 30–60%, "may represent moderate heterogeneity"; 50–90%, "may represent substantial heterogeneity"; 75–100%, "considerable heterogeneity." In cases of outcomes where the null hypothesis of homogeneity was rejected or when there was moderate-to-considerable heterogeneity, a random effects model was used.

The difference in weighted transformed proportions of outcomes between fetoscopic repair and open fetal repair of MMC was analyzed using the Z test. A p value ≤ 0.05 represented statistical significance.

Primary outcomes included overall mortality and VPS placement or ventriculostomy within 12 months of birth. Secondary outcomes included completion of repair via intended access, postnatal treatment for dehiscence or leakage at the MMC repair site, complete reversal of hindbrain herniation, motor response relative to the anatomic level of the lesion, birth <30 weeks' GA, preterm birth (<37 weeks' GA), PROM, CA membrane separation, placental abruption, and uterine dehiscence.

Comparisons were made between fetoscopic and open fetal MMC repair with and without including a study published in 2017 on a modified fetoscopic approach to assess the advantage, if any, of exteriorizing the uterus in fetoscopic surgery. A subanalysis of studies conducted since 2010 was completed to account for the impact of recent advances in both open and fetoscopic techniques.

Table 2. Studies included in the meta-analysis

First author [Ref.]	Year	Country of repair	Type of study	Study period	Surgical approach	Sample size, *n*	Follow-up, years
Graf [26]	2016	Germany	Retrospective	2010–2015	Fetoscopic	71	1
Pedreira [27]	2016	Brazil	Prospective	2013–NS	Fetoscopic	10	1
Degenhardt [28]	2014	Germany	Retrospective	2010–2013	Fetoscopic	51	<1
Verbeek [29]	2012	Germany	Prospective	2003–2009	Fetoscopic	19	0–5
Belfort [24]	2017	USA	Prospective	2014–2016	Fetoscopic	28	<1
Danzer [30]	2016	USA	Retrospective	1998–2003	Open	58	10
Friszer [31]	2016	France	Prospective	2013–2015	Open	3	<1
Moldenhauer [32]	2015	USA	Retrospective	2011–2014	Open	101	<1
Zamłyński [33]	2014	Poland	Prospective	2005–2011	Open	46	1–4
Bennett [34]	2014	USA	Prospective	2011–2013	Open	43	1
Hisaba [35]	2012	Brazil	Prospective	2003–2004	Open	6	3.5

The patients reported on by Degenhart et al. [28] overlap with those reported on by Kohl [12] in 2014, and the patients reported on by Verbeek et al. [29] overlap with those reported on by Kohl et al. [11] in 2010. The preliminary findings reported by Pedreira et al. [13] in 2014 are also reported in 2016 [27], after completion of the study. NS, not specified.

Risk of Bias across Studies

To minimize publication bias and other reporting biases, a comprehensive analysis of all eligible studies was conducted, duplication of data was accounted for, and studies reporting on the same groups of patients were combined.

Results

Study Selection

The systematic review was last conducted in PubMed and Embase on August 13, 2016. We added a study on fetoscopic MMC repair via maternal laparotomy published after completion of the systematic review. Among the studies published since January 1, 2011, using the keywords listed in Data Sources, 438 and 157 records were retrieved from PubMed and Embase, respectively. After screening the title and summary of each retrieved record, 176 records from PubMed and 106 records from Embase were selected as relevant, excluding all records not involving fetal surgical repair of MMC. The relevant records were combined, excluding 84 duplicates. The full-text articles of the remaining 198 records were retrieved and reviewed. After the review, 179 articles were excluded as they were not specific studies of prenatal surgical repair of MMC and related outcomes. These 179 articles were either opinion articles, comments to the editor, or focused instead on the prenatal diagnosis, summary and review of MMC and its treatment, summary of perioperative care, management of urological morbidity, ethical issues surrounding fetal surgery, epidemiology, and translational research. The remaining 19 studies were further assessed for duplication of data, as well as the quality of the reported data. One case report of fetal MMC repair using a cryopreserved umbilical vein was excluded to decrease variability in the treatment strategy [20]. Another case report of fetal MMC repair was excluded as it lacked details regarding the operation performed and subsequent outcomes [21]. Four articles were excluded as they reported follow-up outcomes of the MOMS [8, 9, 22, 23]. We included the outcomes of a recently published study on a modified approach to fetoscopic MMC repair through a maternal laparotomy and excluded a case report by the same authors to avoid duplication of data [24, 25]. Of the remaining 12 articles, 2 were excluded for duplicated data [12, 13]. Eleven studies were therefore selected for inclusion in the meta-analysis (Fig. 1).

Study Characteristics

Among the 11 studies selected for meta-analysis, 5 reported outcomes of fetoscopic repair of MMC and 6 reported outcomes of open fetal repair of MMC (Table 2). The patients reported on by Graf et al. [26], Pedreira et al. [27], Degenhardt et al. [28], Verbeek et al. [29], and Belfort et al. [24] underwent fetoscopic repair of MMC. The patients reported on by Danzer et al. [30], Friszer et al. [31], Moldenhauer et al. [32], Zamłyński et al. [33], Bennett et al. [34], and Hisaba et al. [35] underwent open fetal repair of MMC. For each of the 11 studies, the data

Table 3. Homogeneity analysis for the studies on fetoscopic MMC repair

Outcome	Graf et al. [26]	Verbeek et al. [29]	Pedreira et al. [27]	Degenhardt et al. [28]	Belfort et al. [24]	Homogeneity test
Mortality	5/71	3/16	2/10	4/51	0/22	$Q = 9.97$ $I^2 = 60\%$ $V_\theta = 0.01$
Shunt[1]	32/71	4/13	3/7	NS	9/22	$Q = 0.99$ $I^2 = 0\%$
Function vs. anatomic level[2]	NS	10/13	4/7	NS	16/22	$Q = 0.85$ $I^2 = 0\%$
Completion via intended access	71/71	13/19	8/10	50/51	22/28	$Q = 35.67$ $I^2 = 88\%$ $V_\theta = 0.06$
Postnatal treatment of repair site[3]	20/71	NS	2/8	NS	8/22	$Q = 0.61$ $I^2 = 0\%$
Complete reversal of HH	NS	NS	6/7	NS	12/21	$Q = 2.23$ $I^2 = 55\%$ $V_\theta = 0.03$
Preterm (<37 weeks' GA) birth	63/71	16/16	10/10	47/51	8/22	$Q = 42.59$ $I^2 = 90\%$ $V_\theta = 0.08$
PROM	NS	11/13	10/10	43/51	5/22	$Q = 41.11$ $I^2 = 93\%$ $V_\theta = 0.16$
Uterine dehiscence	NS	NS	0/10	0/51	0/11[4]	$Q = 0$ $I^2 = 0\%$

MMC, myelomeningocele; NS, not specified; HH, hindbrain herniation; GA, gestational age; PROM, premature rupture of membranes. [1] Includes ventriculoperitoneal shunt and other postnatal treatment for hydrocephalus. [2] Proportion of better motor response relative to MMC level. [3] Postnatal treatment for dehiscence at the repair site or cerebrospinal fluid leakage. [4] Dehiscence noted at cesarean section; 11 of the 22 cases reported on by Belfort et al. [24] were delivered vaginally.

reviewed included the study design, sample size, country of operation, operation performed, length of follow-up, and outcomes.

Risk of Bias within Studies

Random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment were not applicable in the 11 selected studies, which are retrospective or nonrandomized prospective cohort studies. Incomplete outcome data were reported by Moldenhauer et al. [32] and Zamłyński et al. [33]. Of the 101 patients who were taken to the operating room for open fetal repair of MMC in the study by Moldenhauer et al. [32], 2 patients were excluded from analysis of the outcomes as these 2 pregnancies were still ongoing. Moldenhauer et al. [32] reported the delivery and neonatal outcomes of only those patients delivered at the Children's Hospital of Philadelphia. Zamłyński et al. [33] reported the rate of VPS placement based on a sample size of only 18 and the rate of reversal of hindbrain herniation based on a sample size of 28 out of an overall study population including 46 patients. Selective reporting of obstetrical or postnatal outcomes was common. Danzer et al. [30] reported neonatal and long-term neurological outcomes but did not report obstetrical outcomes. Graf et al. [26], Verbeek et al. [29], and Friszer et al. [31] did not report the state of the uterine access site or scar at the time of cesarean section. The 5 studies on fetoscopic MMC repair did not report long-term functional outcomes such as ambulation or self-care.

Table 4. Homogeneity analysis for the studies on open fetal MMC repair

Outcome	Moldenhauer et al. [32]	Hisaba et al. [35]	Friszer et al. [31]	Bennett et al. [34]	Zamłyński et al. [33]	Danzer et al. [30]	Homogeneity test
Mortality	6/98	0/6	0/3	3/43	2/46	4/58	$Q = 2.56$ $I^2 = 0\%$
Shunt within 12 months[1]	N/A	2/6	NS	14/41	6/18	26/54	$Q = 2.52$ $I^2 = 0\%$
Function vs. anatomic level[2]	44/80	5/6	NS	NS	NS	NS	$Q = 2.21$ $I^2 = 55\%$ $V_\theta = 0.03$
Completion via intended access	100/101	6/6	3/3	43/43	46/46	58/58	$Q = 2.43$ $I^2 = 0\%$
Postnatal treatment of repair site[3]	3/83	NS	NS	3/41	3/18	NS	$Q = 3.31$ $I^2 = 40\%$ $V_\theta = 0.00$
Complete reversal of HH	59/83	NS	NS	NS	10/28	NS	$Q = 11$ $I^2 = 91\%$ $V_\theta = 0.06$
Preterm (<37 weeks' GA) birth	70/96	6/6	3/3	25/41	38/46	NS	$Q = 15.43$ $I^2 = 74\%$ $V_\theta = 0.02$
PROM	31/96	3/6	1/3	9/41	24/46	NS	$Q = 9.92$ $I^2 = 60\%$ $V_\theta = 0.01$
Uterine dehiscence	7/87	3/6	NS	3/41	6/46	NS	$Q = 6.36$ $I^2 = 53\%$ $V_\theta = 0.01$

MMC, myelomeningocele; NS, not specified; N/A, not applicable; HH, hindbrain herniation; GA, gestational age; PROM, premature rupture of membranes. [1] Includes ventriculoperitoneal shunt and other postnatal treatment for hydrocephalus. Moldenhauer et al. [32] reported shunt placement only up to the time of discharge. [2] Proportion of better motor response relative to MMC level. Zamłyński et al. [33] and Danzer et al. [30] reported functional outcomes such as ambulation but did not specify the precise proportion of patients who had a better motor response relative to the lesion level. [3] Postnatal treatment for dehiscence at the repair site or cerebrospinal fluid leakage.

Synthesis of Results

Homogeneity Test

The studies reporting outcomes of fetoscopic MMC repair were homogenous with regard to the rate of VPS placement or ventriculostomy, motor response relative to the anatomic level of the lesion, postnatal revision or treatment of the MMC repair site, and the state of uterine access sites as observed at cesarean section. There was a moderate-to-substantial degree of heterogeneity between these studies regarding mortality, completion of the operation via the intended access, complete reversal of hindbrain herniation, preterm birth, and other obstetrical outcomes (Table 3).

The studies reporting outcomes of open fetal MMC repair were homogeneous with regard to mortality, VPS placement or ventriculostomy, and completion of the operation via the intended access. These studies showed a moderate-to-considerable degree of heterogeneity for postnatal revision or treatment of the MMC repair site, reversal of hindbrain herniation, motor response relative to the MMC anatomic level, and all obstetrical outcomes. A random effects model was used to calculate the weighted proportion of each outcome in case of heterogeneity (Table 4).

Table 5. Comparison of outcomes: fetoscopic versus open fetal MMC repair

Outcome	Fetoscopic		Open mean ES, % (95% CI)	*p* value (*Z* test)	
	mean ES w/o Belfort, % (95% CI)	mean ES w/ Belfort, % (95% CI)		w/o Belfort	w/ Belfort
Mortality	9 (5, 14)	7 (2, 15)	6 (3, 9)	0.20	0.65
Shunt	43 (33, 53)	42 (33, 52)	40 (32, 49)	0.71	0.73
Completion via intended access	92 (74, 100)	**90 (72, 99)**	**99.8 (99, 100)**	0.08	**0.02**
Reversal of HH	86 (53, 100)	69 (39, 93)	54 (21, 86)	0.18	0.52
Functional vs. anatomic level	70 (49, 89)	72 (57, 84)	56 (46, 67)	0.24	0.09
Postnatal treatment of repair site	**28 (19, 38)**	**30 (21, 39)**	**7 (2, 13)**	**<0.01**	**<0.01**
Delivery <30 weeks' GA	22 (8, 39)	17 (7, 32)	13 (3, 28)	0.39	0.61
Preterm birth (<37 weeks' GA)	**96 (88, 100)**	90 (69, 100)	**81 (66, 92)**	**0.04**	0.43
PROM	**91 (74, 99)**	**79 (40, 99)**	**36 (24, 49)**	**<0.01**	**0.04**
CA membrane separation	17 (0, 61)	21 (2, 52)	9 (0, 32)	0.70	0.46
Placental abruption	2 (0, 18)	3 (0, 17)	3 (1, 5)	0.83	0.85
Uterine dehiscence	**0 (0, 2)**	**0 (0, 1)**	**11 (5, 20)**	**<0.01**	**<0.01**

Bold type denotes significance. Mean ES, mean effect size or weighted proportion of outcome; w/ or w/o Belfort, including or excluding the 2017 study by Belfort et al. [24] with fetoscopic MMC repair via maternal laparotomy rather than percutaneous access; GA, gestational age; PROM, premature rupture of membranes; CA, chorioamniotic; MMC, myelomeningocele; HH, hindbrain herniation.

Primary Outcomes

There was no significant difference in combined fetal and postnatal mortality between fetoscopic (7%) and open repair (6%, $p = 0.65$). There was no significant difference in the rate of VPS placement or ventriculostomy within 12 months of birth between fetoscopic (42%) and open repair (40%, $p = 0.73$) (Table 5). The subanalysis of the studies conducted since 2010 supported these findings (Table 6).

Secondary Outcomes

The differences between fetoscopic and open surgical approaches were not statistically significant for reversal of hindbrain herniation, motor response relative to the MMC anatomic level, birth <30 weeks' GA, CA membrane separation, and placental abruption when considering only outcomes of fetoscopic surgery performed percutaneously or when combining those outcomes with those of fetoscopic surgery via a maternal laparotomy.

Overall, fetoscopic MMC repair was associated with higher rates of dehiscence or CSF leakage from the MMC repair site requiring postnatal treatment (30 vs. 7%, $p < 0.01$) and of PROM (79 vs. 36%, $p = 0.04$). The rate of uterine dehiscence was higher following open repair (11 vs. 0%, $p < 0.01$) (Table 5).

Percutaneous fetoscopic MMC repair was associated with a higher rate of preterm birth compared to open repair (96 vs. 81%, $p = 0.04$). When combining the outcomes of percutaneous and fetoscopic repair via maternal laparotomy, the difference in the rate of preterm birth between fetoscopic and open repair was not statistically significant. When combining the outcomes of both fetoscopic approaches, the difference in number of cases completed via the originally intended access between the fetoscopic (90%) and the open approach (99.8%, $p = 0.02$) was statistically significant.

The subanalysis of the studies conducted since 2010 supported these findings, with the exception that the differences between combined outcomes of both fetoscopic approaches and the open approach were not statistically significant with regard to PROM (Table 6).

Discussion

We compared the outcomes of two different maternal-fetal surgical approaches for fetal repair of MMC. After weighting the proportion of each outcome across the studies on fetoscopic surgery and open surgery, we found that both surgical approaches were associated with com-

Table 6. Subanalysis of the studies conducted since 2010

Outcome	Fetoscopic		Open mean ES, % (95% CI)	*p* value (*Z* test)	
	mean ES w/o Belfort, % (95% CI)	mean ES w/ Belfort, % (95% CI)		w/o Belfort	w/ Belfort
Mortality	8 (4, 13)	6 (1, 14)	6 (3, 10)	0.51	0.86
Shunt	45 (34, 56)	44 (34, 54)	34 (21, 49)	0.25	0.27
Completion via intended access	98 (88, 100)	94 (79, 100)	99 (98, 100)	0.43	0.14
Reversal of HH	86 (53, 100)	69 (39, 93)	71 (61, 80)	0.36	0.91
Functional vs. anatomic level	57 (22, 87)	69 (51, 84)	55 (44, 66)	0.91	0.18
Revision of MMC	**28 (19, 38)**	**30 (21, 39)**	**5 (2, 9)**	**<0.01**	**<0.01**
Delivery <30 weeks' GA	13 (8, 19)	11 (7, 17)	8 (4, 12)	0.15	0.26
Preterm birth (<37 weeks' GA)	**93 (84, 98)**	85 (60, 99)	**73 (55, 87)**	**0.02**	0.38
PROM	**95 (66, 100)**	77 (25, 100)	**29 (22, 37)**	**<0.01**	0.07
CA membrane separation	17 (0, 61)	21 (2, 52)	6 (0, 46)	0.63	0.46
Placental abruption	2 (0, 18)	3 (0, 17)	2 (0, 5)	0.91	0.76
Uterine dehiscence	**0 (0, 1)**	**0 (0, 1)**	**8 (4, 13)**	**<0.01**	**<0.01**

Bold type denotes significance. Mean ES, mean effect size or weighted proportion of outcome; w/ or w/o Belfort, including or excluding the 2017 study by Belfort et al. [24] with fetoscopic MMC repair via maternal laparotomy rather than percutaneous access; GA, gestational age; PROM, premature rupture of membranes; CA, chorioamniotic; MMC, myelomeningocele; HH, hindbrain herniation.

parable rates of mortality, VPS placement or ventriculostomy, reversal of hindbrain herniation, motor response relative to the MMC anatomic level, CA membrane separation, and placental abruption. We found a higher rate of PROM and preterm birth following percutaneous fetoscopic repair compared to open repair. The difference in the rate of preterm birth was not significant when the outcomes of percutaneous fetoscopic repair and those of fetoscopic repair via maternal laparotomy were combined. There was a tendency toward a higher rate of premature delivery <30 weeks' GA after fetoscopic MMC repair. Postnatal operative revision of MMC repair and nonoperative treatment for dehiscence or leakage at the repair site were required more frequently after fetoscopic MMC repair. The state of the uterine port sites or hysterotomy scar at the time of cesarean section was selectively reported. The rate of uterine dehiscence was higher after open fetal MMC repair. To account for the impact of recent advances in both open and fetoscopic techniques, a subanalysis of the studies conducted since 2010 was completed and supported these findings.

Both surgical approaches resulted in VPS placement or ventriculostomy rates comparable to those of the MOMS: 43% following percutaneous fetoscopic repair, 42% following both percutaneous and fetoscopic repair via maternal laparotomy, 40% following open repair, and 40% in the MOMS prenatal repair group [7]. Only 2 studies on fetoscopic repair [24, 27] and 2 studies on open repair [32, 33] clearly reported rates of complete reversal of hindbrain herniation (69 and 54%, respectively), all of which appear higher than the rate in the MOMS prenatal repair group (36%). The results of postnatal neurologic examination assessing motor response relative to the MMC level were not different between fetoscopic and open repair. However, no long-term cognitive and functional outcomes have been reported in the studies on fetoscopic MMC repair.

One of the concerns raised regarding the outcomes of the MOMS was the high rate of obstetrical complications and premature birth in the prenatal repair group. Adzick et al. [7] reported 26% CA membrane separation, 6% placental abruption, 25% uterine scar thinning, 10% dehiscence of the hysterotomy closure, and only 21% term birth (≥37 weeks' GA). Follow-up analyses of obstetrical outcomes of the MOMS led to the conclusion that the high rate of preterm PROM (30.7%), premature birth, and other obstetrical complications may be reduced by innovations in minimally invasive fetoscopic repair of MMC [8, 9]. An additional concern regarding open fetal surgery is the requirement of cesarean delivery in sub-

sequent pregnancies because of the potential for uterine rupture. Vaginal delivery after a cesarean is avoided following hysterotomy for fetal surgery [36]. The fetoscopic approach has been suggested as an alternative with possibly better obstetrical outcomes [25].

The notion that the fetoscopic approach may reduce the rate of obstetrical complications and premature birth after fetal repair of MMC has been challenged with reports of an increased risk of membrane rupture, premature birth, and inability to reliably obtain a watertight closure of the MMC defect with fetoscopic surgery, requiring postnatal revision of the repair [18]. In an opinion article, Flake [17] raises concerns over the minimally invasive technique utilized by Kohl and his colleagues at the German Center for Fetal Surgery and Minimally Invasive Therapy, where the largest number of fetoscopic MMC repairs was performed. Concerns regarding the prolonged operative time, the high rate of amniotic fluid leakage and membrane separation, the high rate of preterm birth, and the inability to consistently achieve a watertight closure of the MMC defect were echoed by 2 subsequent reviews [14, 15].

For fetoscopic MMC repair to be considered a better alternative to open repair, it should result in similar – if not superior – obstetrical, neonatal, and long-term neurodevelopmental outcomes. Centers that perform fetal repair of MMC tend to utilize one approach or the other. There were no original studies in the literature, retrospective or prospective, comparing outcomes of fetoscopic versus open fetal MMC repair from a single center. Therefore, the comparison of outcomes of these two surgical approaches relies on meta-analyses of published data from various fetal surgery centers [37]. Three prior meta-analyses compared outcomes of fetoscopic and open MMC repair. Araujo Júnior et al. [38] found that both approaches are associated with comparable rates of VPS placement; however, they did not address obstetrical complications. In a separate meta-analysis, in which cohorts with less than 10 cases were excluded, Araujo Júnior et al. [39] concluded that while the fetoscopic approach avoids the risk of hysterotomy scar thinning and dehiscence, it is associated with higher rates of obstetrical complications and premature birth compared to the open approach. However, because fetal MMC repair is performed in only a small number of centers around the world, including small cohorts will account for outcomes in countries such as Brazil and France, where the cohorts are small [40]. Joyeux et al. [41], in a separate meta-analysis, found similar results. Their meta-analysis design, however, was limited by comparing fetoscopic repair performed both before and after the MOMS with only the results from the MOMS, excluding the post-MOMS studies on open surgery. The selective exclusion of post-MOMS open repairs limits the applicability of their results to the most up-to-date open fetal techniques that have since been developed in the post-MOMS era.

To address the limitations of these prior meta-analyses, we conducted a systematic review of the post-MOMS literature and included large and small cohorts with reported outcomes of fetal MMC repair. The results of this study corroborate those of the prior meta-analyses when considering percutaneous fetoscopic MMC repair. We added a more recent study by Belfort et al. [24] to the meta-analysis to determine if fetoscopic access via maternal laparotomy made a difference, and we found that combining outcomes of both fetoscopic approaches resulted in lower rates of preterm birth. However, the rate of dehiscence or leakage at the MMC repair site was high following both fetoscopic approaches.

This study is limited by several factors including incomplete outcome data from some studies, selective reporting of outcomes within each study, utilization of only one surgical approach at each maternal-fetal center, and variability in surgical techniques by center.

The outcome variables analyzed in this meta-analysis were not all reported in each study. Only 3 of the 5 articles on fetoscopic surgery [25, 28, 29] reported the rate of dehiscence or leakage at the MMC repair site. Only 2 of the 6 studies on open repair [32, 33] and 2 of the 5 studies on fetoscopic repair [25, 27] reported the rate of complete reversal of hindbrain herniation, making a comparison difficult to interpret.

Three of the largest series of fetoscopic MMC repair reported in the literature included patients who underwent fetoscopic MMC repair at the German Center for Fetal Surgery and Minimally Invasive Therapy [26, 28, 29]. The operative technique used at the German center was pioneered by Thomas Kohl in 2006 [42] and involves maternal transabdominal ultrasound-guided placement of three percutaneous intrauterine 5-mm trocars, partial evacuation of amniotic fluid and carbon dioxide insufflation (PACI), dissection of the neural placode, coverage of the spinal cord with at least one collagen/Teflon patch, demonstration of watertight coverage by observing bulging of the patch, removal of carbon dioxide, refilling of the amniotic cavity with isotonic solution, and closure of the abdominal trocar insertion sites [12] (Table 7).

Another series, the Cirurgia endoscópica para correção antenatal da meningomielocele em humanos (CECAM) trial, reports outcomes of patients who under-

Table 7. Fetoscopic techniques

Study [Ref.]	Access	Uterine ports; insufflation	Dissection of neural placode	MMC coverage	Port site closure	Operative time, min
Graf [26][1] Degenhardt [28][1] Verbeek [29][1]	Percutaneous	5-mm ports (×3); PACI	Yes	Collagen/Teflon patch Skin mobilized to cover free edges of patch	NS[2]	98–480
Pedreira [27]	Percutaneous	4- to 5-mm ports (×3); PACI	Yes	Biocellulose patch Primary (or patch) skin closure	None except 1st case (GORE HELEX devices)	145–450
Belfort [24]	Laparotomy	4-mm ports (×2)[3]; PACI	Yes	Primary closure incorporating dura and skin	Yes, with suture	107–434

MMC, myelomeningocele; PACI, partial amniotic carbon dioxide insufflation after partial withdrawal of amniotic fluid; NS, not specified. [1] Performed at the German Centre for Fetal Surgery and Minimally Invasive Therapy in Germany, at the University of Giessen-Marburg [26, 28], and at the University of Bonn [29], all utilizing the methods described by Thomas Kohl. [2] Degenhardt et al. [28] report that the trocar sites were closed, but the method of closure is not specified. [3] Three ports rather than 2 were used in 6 patients.

went fetoscopic MMC repair in São Paulo, Brazil. In their series, Pedreira et al. [27] report a modified technique that involves placing a biocellulose patch over the spinal cord rather than the collagen/Teflon patch used by Kohl and closure of the fetal skin over the patch. Like Kohl, they used PACI. They also report leaving the uterine trocar sites open based on complications related to the first case in the CECAM trial, in which the trocar sites were closed with GORE HELEX devices. This case was complicated by PROM, preterm delivery at 32 weeks' gestation, dislodgement of the closure devices, and enlargement of the trocar sites to 2–3 cm each observed at the time of cesarean delivery [13] (Table 7).

Early cases of in utero repair of MMC used either the fetoscopic or the open approach. In the USA, the fetoscopic approach was initially reported by Bruner et al. [43] at Vanderbilt University in 1997 and by Farmer et al. [44] at the University of California, San Francisco, in 2003. However, due to high initial complication rates associated with fetoscopic MMC repair, in addition to the necessity of a standardized surgical approach for a clinical trial comparing outcomes of prenatal versus postnatal repair, fetoscopic MMC repair was temporarily halted in the USA. The standardized approach used in the MOMS is the gold standard for fetal MMC repair and involves a maternal laparotomy, a hysterotomy, dissection of the neural placode, watertight closure of the dura, and closure of the fetal skin as described by Adzick et al. [7]. Open fetal MMC repair performed in the USA, France, Poland, and Brazil includes these fundamental steps [31–35, 45].

Belfort et al. [24] at Texas Children's Fetal Center describe a fetoscopic approach that mitigates the complications of both percutaneous fetoscopic and open fetal MMC repair. Like Kohl, they used PACI. Unlike Kohl or Pedreira et al. [27], they accessed the uterus though a maternal laparotomy and completed the operation using two 4-mm uterine ports after securing the membranes against the uterine wall with sutures and closed the uterine port sites primarily with absorbable sutures. They dissected the neural placode and primarily closed both the dura and the skin as a single layer over the spinal cord, which they did not cover with a patch (Table 7). Their approach resulted in 100% fetal and neonatal survival and only 36% birth <37 weeks' GA, which is lower than in any previously reported cohort of fetal MMC repair. Theirs was the first reported cohort study that demonstrated the possibility of vaginal delivery (50%) after fetal MMC repair. Overall, fetoscopic MMC repair via maternal laparotomy, as described by Belfort et al. [24], resulted in better obstetrical outcomes compared to either standard open repair or the percutaneous fetoscopic approach, and in comparable fetal and neonatal outcomes, except for CSF leakage requiring revision of the MMC repair in 36% of the cases.

All reported births following percutaneous fetoscopic or open fetal MMC repair were by cesarean section. Exposure of the uterus theoretically should allow assessment of the uterine trocar sites or hysterotomy scar, but studies on percutaneous fetoscopic MMC repair selectively reported the appearance of the uterine trocar sites. Because of such selective reporting, comparing the rate of

thinning or dehiscence of the uterine access site is unreliable. Graf et al. [26], for example, did not describe the appearance of the uterine trocar sites. Degenhardt et al. [28], on the other hand, reported intact and well-healed uterine trocar sites in all cases. Pedreira et al. [27] reported no evidence of myometrial thinning or dehiscence in the final report of the CECAM trial. However, a report of preliminary results describes enlargement of the uterine trocar sites to 2–3 cm each in 1 case [13]. In addition, studies selectively report whether the uterine trocar site was closed or left open. It is not possible to clearly determine that percutaneous fetoscopic MMC repair eliminates the risk of thinning or dehiscence of the uterine access site unless the state of the uterine access site at the time of cesarean section is consistently assessed and reported. Belfort et al. [25], on the other hand, reported that they uniformly closed all uterine port sites with absorbable sutures, and noted at the time of cesarean delivery that all port sites were well healed.

The operative time is a factor, in addition to the type of uterine access, which may impact obstetrical and neonatal outcomes after fetal MMC repair. A concerning aspect of the fetoscopic approach is the duration of carbon dioxide insufflation of the amniotic cavity and the overall duration of the operation, i.e., 98–480 min for the percutaneous approach [27, 28] and 145–450 min for fetoscopic repair via maternal laparotomy, in comparison to 54–130 min needed for open fetal MMC repair [32, 46]. A prolonged operative time has been reported as a potential factor contributing to PROM, which may explain the higher rate of PROM after fetoscopic MMC repair in this meta-analysis [9, 27].

In conclusion, based on the results of our meta-analysis, the major limitations of fetoscopic MMC repair are PROM and a high rate of dehiscence or leakage at the MMC repair site requiring postnatal revision. The percutaneous fetoscopic approach to MMC repair may offer a better alternative to the open approach if the technique can be optimized to overcome preterm birth, PROM, and the need for postnatal revision of the repair. GA at birth is improved with better handling of the membranes and primary closure of the uterine port sites, as seen when fetoscopic MMC repair is achieved via maternal laparotomy. Long-term cognitive, behavioral, and functional outcomes of fetoscopic MMC repair have yet to be reported and compared to the gold standard of open fetal MMC repair. Following open fetal surgery, cesarean section is required for delivery in subsequent pregnancies because of the potential for uterine rupture. Based on the outcomes of fetoscopic MMC repair via maternal laparotomy as described by Belfort and colleagues, fetoscopic MMC repair allows spontaneous vaginal delivery.

Based on the results of our meta-analysis, the current techniques in fetoscopic surgery should be optimized to achieve a watertight closure of the MMC defect that is comparable to open repair. Centers practicing percutaneous fetoscopic MMC repair might adopt the techniques employed by Belfort and colleagues for intrauterine access and port site closure to improve obstetrical outcomes.

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Disclosure Statement

The authors declare no conflicts of interest.

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