Received: 28 July 2020 | Revised: 5 January 2021 | Accepted: 27 January 2021

DOI: 10.1002/nau.24629

ORIGINAL CLINICAL ARTICLE

Neurourology and Urodynamics | ICS | SUFU | WILEY

Prevalence of high-risk bladder categorization with prenatal and postnatal myelomeningocele repair types

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Abstract

Introduction: Urologic substudies of prenatal myelomeningocele (MMC) closure have focused primarily on continence without significant clinical benefit. Fetoscopic MMC repair (FMR) is a newer form of prenatal intervention and touts added benefits to the mother, but urological outcomes have yet to be analyzed. We set out to focus on bladder safety rather than continence and examined bladder outcomes with different prenatal MMC repairs (FMR and prenatal open [POMR]) and compared bladder-risk-categorization to traditional postnatal repair (PSTNR).

Methods: An IRB-approved retrospective analysis of all patients undergoing all forms of MMC repairs with inclusion and exclusion criteria based on the MOMS trial was performed. Bladder safety assessment required initial urodynamic studies (UDS), renal bladder ultrasound (RBUS), and/or voiding cystourethrogram (VCUG) within the 1st year of life. Follow-up analyses within the cohorts required follow-up studies within 18 months after initial evaluations. Outcomes assessed included bladder-risk-categorization based on the CDC UMPIRE study (high, intermediate, and safe), hydronephrosis (HN), and vesicoureteral reflux (VUR). A single reader evaluated each UDS.

Results: Initial UDS in 93 patients showed that the prevalence of high-risk bladders were 35% FMR versus 36% PSTNR and 60% POMR. Follow-up UDS showed only 8% of FMR were high-risk compared to 35% POMR and 36% PSTNR. Change from initial to follow-up bladder-risk-category did not reach significance ($p = .0659$); however, 10% PSTNR worsened to high-risk on follow-up, compared to none in either prenatal group. Subanalysis of follow-up UDS between the prenatal cohorts also was not significant ($p = .055$). Only 8% of FMR worsened or stayed high-risk compared to 35% with POMR ($p = .1$). HN was significantly different at initial and subsequent follow up between the groups with the least in the FMR group.

Conclusions: Early outcome UDS analyses demonstrated lower incidence of high-risk bladders in FMR patients with a trend toward clinically significant improvement compared to POMR in regard to all evaluated metrics. Larger,

prospective, confirmatory studies are needed to further evaluate the potential benefits on FMR on bladder safety and health.

KEYWORDS
fetoscopic repair, Myelomeningocele, neurogenic bladder, prenatal repair, spina bifida

1 | INTRODUCTION

Spina bifida (SB) remains the most common permanently disabling birth defect in the United States. Birth prevalence is estimated at 3.4 per 10,000 live births with Hispanic women having the highest rate of affected children.[1,2] Major disabilities are common within this population—affecting many organ systems including neurocognitive, musculoskeletal, gastrointestinal, orthopedic, and urologic. Repair of SB has evolved drastically from its initial description in the 1600s,[3] yet the most common repair type around the world remains the traditional open postnatal closure (PSTNR) of the neural tube defect. Given the irreversible nature of spinal cord and peripheral nerve damage with this disease, surgical approach to SB closure has evolved to prenatal open in-utero myelomeningocele repair (POMR) in an effort to minimize the duration of damage to these vital structures. The most recent surgical advancement, popularized at our institution, is the laparoscopic approach to SB repair, known as fetoscopic myelomeningocele repair (FMR).[4]

The Management of Myelomeningocele Study (MOMS) is a landmark study, which demonstrated benefit to prenatal intervention with MMC closure. Prenatal intervention was associated with a significant reduction in the need for cerebrospinal fluid shunts and greatly reduced the rates of hindbrain herniation at 1 year of age.[5] From a functional standpoint, prenatal surgery also resulted in the improvement in mental development scoring and overall motor function.[5-7] Despite these tremendous neurosurgical and motor benefits, the MOMS trial did not find any improvement in bladder continence and the severity of urologic sequelae appears to be independent of the severity of deficit seen in other systems and similarly, appears independent of the degree of improvement in other systems. Early studies have reported significant benefit to prenatal repair on bladder function in terms of voiding patterns.[8-14] Recent urological follow up in school-age children from the MOMS trial did not show any definitive continence improvement although families of patients reported less need for clean intermittent catheterization in prenatal repair patients.[15]

Two main goals exist in the urologic care of SB: (1) obtaining safe bladder pressure to minimize risk of renal damage; and (2) establishing eventual social continence. Both of these overarching urological goals are important, but the establishment of a "safe" bladder with minimization of risk toward chronic kidney disease (CKD) should be the initial objective. Previous studies examing the urologic benefits with prenatal SB intervention, focused on social continence as the main urological outcome rather than bladder safety or hostility. Although improvement of social continence with prenatal interventions would be significantly impactful in the quality of life of MMC patients, safer bladder parameters on UDS would seem to be the logical primary goal.

Subsequently, we sought to answer the more clinically beneficial question of whether prenatal repair, especially fetoscopic repair, is associated with a reduction in high-risk bladder categorization noted on UDS at initial lower urinary tract (LUT) evaluation and follow up. Bladder-risk stratification outcome, particularly a hostile bladder, is directly correlated with progression of CKD and need for bladder reconstruction. Subsequently, our goal was to evaluate the urodynamic bladder risk categorization for each of the three types of SB repair performed at our institution—postnatal open, prenatal open, and prenatal fetoscopic. We hypothesize that FMR has potential to result in safer bladder UDS outcomes due to less traumatic early MMC repairs.

2 | METHODS

Using an Institutional Review Board approved database, we performed a retrospective analysis of all patients with repaired myelomeningocele at our institution. Patient selection for prenatal intervention followed the same criteria as the MOMS trial (Figure 1). We similarly matched our postnatal cohort utilizing these same criteria including the same MMC lesion level requirements. Analysis of specific levels of lesions was not possible due to the heterogeneous distribution within each of the MMC repair cohorts.

Urological evaluation included baseline renal bladder ultrasound (RBUS), cystometrogram (CMG), and/or voiding cystourethrogram within the 1st year of life. Because of our specialized care center's prenatal MMC repair experience, patients would travel outside of our city and state for their MMC repair. Some of the patients would undergo their urological evaluation studies with their local pediatric urologist. Subsequently, there was a

FIGURE 1 Details regarding the inclusion and exclusion criteria utilized in the MOMS trial which were applied to the cohort studied in this review

Inclusion Criteria

- Myelomeningocele (MMC) at T1 through S1 with hindbrain herniation, level of MMC confirmed by ultrasound and hindbrain herniation confirmed by MRI
- Maternal age greater than or equal to 18 years
- Gestational age 19 0/7 weeks to 25 6/7 weeks at the time of prenatal surgery
- Normal karyotype or FISH
- Normal fetal echocardiogram
- Singleton pregnancy
- Willing to remain close to Texas Children's Hospital

Exclusion Criteria

- Significant fetal anomaly not related to MMC
- Kyphosis in fetus of greater than 30 degrees
- History of incompetent cervix, cervix less than 20mm in length or presence of a cerclage
- Morbid obesity as defined as a BMI of greater than 35
- Maternal-fetal Rh isoimmunization, Kell sensitization or a history of neonatal alloimmune thrombocytopenia
- Maternal HIV, Hepatitis B, Hepatitis C due to increased risk of transmission to the fetus during maternal-fetal surgery
- Uterine anomaly such as large or multiple uterine fibroids or mullerian duct abnormality
- Maternal medical condition which is a contraindication to abdominal surgery or general anesthesia
- No support person to stay with mother at Ronald McDonald House
- Patient does not meet psychosocial criteria as determined by the social worker evaluation
- Previous hysterotomy in the active segment of the uterus either from previous classical cesarean section or uterine anomaly such as an arcuate or bicornuate

lack of uniformity in each of the urological evaluations. Having any of the three tests within the 1st year of life would qualify the patient for inclusion in the total for that particular outcome analysis. Follow-up studies needed to be completed within 18 months after baseline testing to track progression, without the requirement that all three studies be obtained. Because some patients treated prenatally lived far away from our region and did not necessarily follow up at our institution, patients included in the initial study cohort did not necessarily have follow up studies and thus were not necessarily within the follow-up cohort. RBUSs and VCUGs were read by the radiologists at our institution. All CMGs were read by a single reviewer, blinded as to the repair type.

Radiological outcomes were reported in a binary fashion. RBUSs were appraised for the presence or absence of hydronephrosis (HN). The complete absence of HN was determined by the radiologist's report explicitly stating "no hydronephrosis present" with any other terminology consistent with the presence of HN being deemed as positive for HN, regardless of grade. Bladder fullness was not taken into account in regard to HN presence or absence. VCUG results were assessed for the presence or absence of vesicoureteral reflux (VUR). CMGs were evaluated based on multiple factors, which comprise the bladder risk categorizations outlined in Figure 2 and are modeled after the protocol used by the Centers for Disease Control (CDC) Urologic Management to Preserve Initial Renal Function Protocol (UMPIRE) in newborn and young children with spina bifida. Hostile bladder is defined as end filling pressure or DLPP 40 cm H2O or greater, or neurogenic detrusor overactivity (NDO) with detrusor sphincter dyssynergia (DSD). Intermediate risk is defined as end filling pressure or DLPP 25–39 cm H2O with NDO, but without DSD. Abnormal but safe is defined as end filling pressure or DLPP less than 25 cm H2O with no DSD or NDO. A normal bladder is defined as normal capacity, end filling pressure of DLPP < 15 cm H2O with no NDO or DSD, and minimal postvoid residual.[16] Similar to the imaging analyses, a subanalysis of the CMGs included a simplified comparison of high-risk and non-high-risk bladders by combining low risk and intermediate-risk categories, as these patients do not require surgical intervention and have not fully failed standard clinical management of clean intermittent catheterization (CIC) and anticholinergics (ACh). LUT management specifics (CIC and/or ACh use) were not investigated secondary to heterogeneity with LUT management regimens.

All CMGs were performed according to the standards of good practice as set forth by the International Continence Society and the International Children's Continence Society.[17,18]

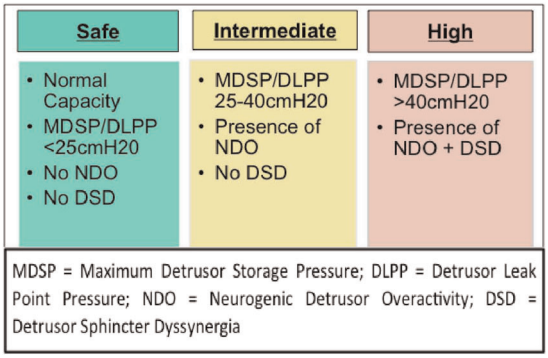

FIGURE 2 Details regarding the criteria for categorizing bladder risk based on urodynamic findings

All statistical analyses were performed by our institution's statistics department. Fisher's exact tests, Kruskal–Wallis test, and Mann–Whitney *U* test were used for nonparametric and nonnormally distributed data. A p value $< .05$ was considered statistically significant. Additionally, odds ratios were calculated to compare fetoscopic repair to the other surgical modalities in terms of likelihood of initial high-risk bladders and likelihood of improving from or staying less than high-risk.

3 | RESULTS

Ninety-three patients met inclusion and exclusion criteria, which can be found in Figure 1. Distribution of MMC repair types and testing during the study are shown in Table 1.

3.1 | Stratification by anatomic lesion

Additional data analysis evaluated the breakdown of patients based on lesion level (Table 2, Figures 3 and 4). Five patients had sacral MMC, 9 patients thoracic, and 73 with lumbar level lesions. Among thoracic lesions, four/nine were initially high risk and three/eight with follow-up studies remained high while one improved from high. For sacral level lesions, three/five were initially high risk, of which two remained high risk, and one improved from high risk. For the lumbar level lesions, 28/73 were initially high risk while 15/52 with follow-up studies remained or worsened to high risk and 15 improved from high risk. Given the small cohort size of the sacral and thoracic groups, statistical analysis by lesion level was not pursued.

3.2 | Stratification of lesion level by intervention timing

Among initial studies, the prenatal open cohort included one sacral lesion and one thoracic level lesion with the remainder being lumbar. Within the postnatal cohort there were seven thoracic level lesions and four sacral level lesions. Across the fetoscopic group, there was one thoracic level lesion.

TABLE 1 Breakdown of repair type numbers and associated studies

	Initial studies	Follow-up studies
POMR	20	17
FMR	22	13
PSTNR	51	39

Abbreviations: FMR, fetoscopic myelomeningocele repair; POMR, prenatal open in-utero myelomeningocele repair; PSTNR, postnatal repair.

TABLE 2 Percentage of high-risk bladders per lesion level, initial, and follow up

	Initial high risk	Follow-up high risk
Thoracic	44%	38%
Lumbar	38%	29%
Sacral	60%	50%

3.3 | Stratification of UDS by intervention timing

Initial UDS bladder risk categorization showed increased prevalence of high-risk bladders in the POMR group (60%) compared to the other MMC repair-types (PSTNR 36%; FMR 33%). Amongst those patients with follow up studies, follow-up UDS showed only 8% of FMR bladders were high-risk (improved from 33%) compared to higher prevalence seen in the other MMC repair-types: 35% POMR (improved from initial 60%) and 36% PSTNR (stable from initial 36%; $p = .15$; Table 3, Figures 5 and 6). Subanalysis was then performed combining categories into either high-risk or not high-risk. We combined the safe and intermediate bladders into the not high-risk group and compared these bladders with the prevalence of high-risk and found that we did not reach statistical significance although there was less high-risk or "hostile" bladders within the fetoscopic group (7.7%) compared to the nonfetoscopic group (35% POMR and 36% PSTNR; Table 3).

With our longitudinal follow-up on UDS measuring bladder risk, we found no significant proportional changes amongst the groups from initial to follow up UDS ($p = .0659$). Interestingly, 10% of the PSTNR group worsened their bladder risk categorization in comparison to none in either of the prenatal repair groups (Table 3, Figure 7).

Odds ratios were then calculated to compare the odds of high-risk bladder outcomes in the fetoscopic versus nonfetoscopic groups (either PSTNR or POMR). We found that the PSTNR group was 6.7 times more likely to have initial high-risk bladder compared to FMR-treated patients; however, this did not achieve statistical significance (CI 0.78–57.25, $p = .0814$). Additionally, POMR-treated patients were 6.5 times more likely to be categorized as high-risk bladders compared to FMR patients (CI 0.68–63.33, $p = .1047$; Table 4). We then calculated the odds ratios to compare the likelihood of

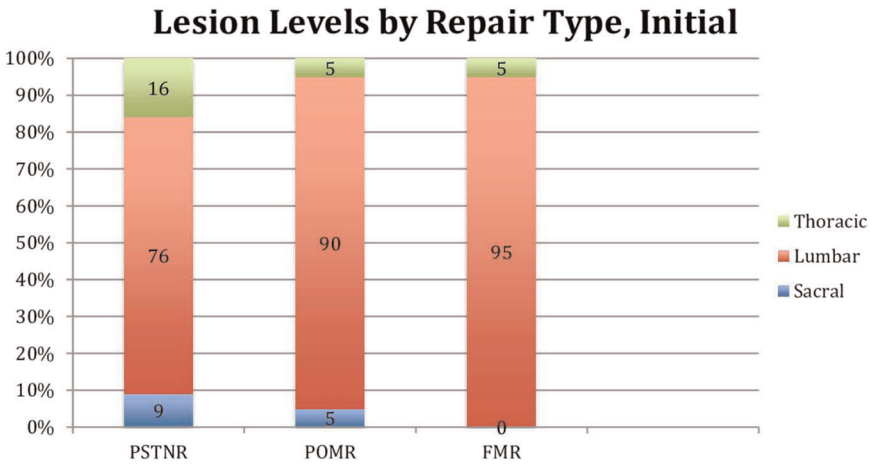

FIGURE 3 A visual representation of the lesion level prevalence within each repair type studied at the time of initial studies

improvement from high-risk or remaining at a non-high-risk bladder status on follow-up UDS. Both PSTNR and POMR were 85.1% and 84.7% (respectively) less likely to improve from high-risk or remain non-high-risk as compared to FMR (Table 4).

We then compared only the prenatal repair types and excluded the PSTNR cohort and performed a subanalysis of the initial and follow-up UDS in the FMR versus POMR cohorts. Within the prenatal intervention groups, we found that 8 fetoscopic patients (36%) had high-risk bladder categorization on initial UDS in comparison to 12 open-repaired patients (60%; $p = .055$). On follow-up UDS, one patient (7.7%) of the FMR cohort remained with a high-risk bladder in comparison to six patients (35%) with unchanged high-risk bladders from the POMR group ($p = .1$; Table 5).

Other outcome parameters associated with bladder hostility were evaluated including VUR and HN. VCUG testing demonstrated the presence of VUR in 18% PSTNR, 5% POMR, and 14% FMR cohorts at baseline. There was an increase in the prevalence of VUR on follow-up in the PSTNR and POMR groups (44.6% and 50%, respectively) whereas there was essentially no change, at 13%, in the fetoscopic group, but this did not meet statistical significance ($p = .626$). When we examined the presence of HN in our MMC-repaired groups, we found significant distribution differences for the presence of HN at initial and follow-up RBUS across the groups (31% PSTNR, 10% POMR, 0% FMR, $p = .0015$% and 24% PSTNR, 0% POMR, 0% FMR, $p = .005$, respectively; Table 3).

Finally, we accounted for the gestational age at delivery between the different MMC repair types. The PSTNR and FMR cohorts were found to have identical gestational ages at delivery (37.3 weeks) whereas the POMR cohort was found to have a significantly younger gestational age at delivery of 35.9 weeks ($p = .0065$; Figure 8).

4 | DISCUSSION

Our institution is one of the few in the world performing fetoscopic repair, which has been demonstrated to maintain the neurologic and motor outcomes benefit of

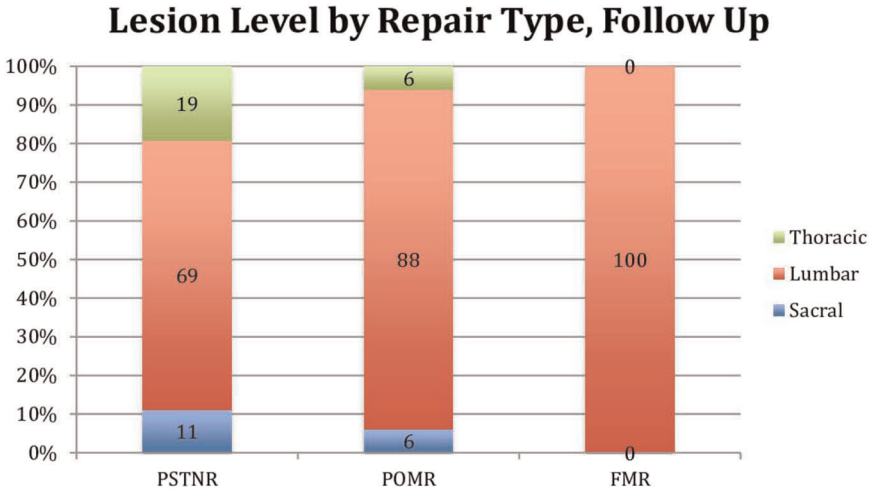

FIGURE 4 A visual representation of the lesion level prevalence within each repair type studied at the time of follow-up studies

TABLE 3 Comparison of all MMC repair types

	Risk categorization	Postnatal		Prenatal open		Fetoscopic		
		Available N	Count (%)	Available *N*	Count (%)	Available *N*	Count (%)	*p*
Follow-up UDS	Normal/ abnormal Safe	39	9 (23)	17	4 (24)	13	5 (38)	.37
	Intermediate		16 (41)		7 (41)		7 (54)	
	High		**14 (36)**		**6 (35)**		**1 (7.7)**	
Follow up UDS (high risk vs normal/ abnormal safe + intermediate)	High	39	14 (36)	17	6 (35)	13	1 (7.7)	.15
Initial to follow-up UDS change	**Worsened to high**	39	**4 (10)**	17	**0 (0)**	13	**0 (0)**	.0659
	Stayed high		10 (26)		6 (35)		1 (7.7)	
	Improved from high		5 (13)		6 (35)		6 (46)	
	Same or stayed less than high		20 (51)		5 (29)		6 (46)	
HN on initial RBUS	Present	51	16 (31)	20	2 (10)	22	0 (0)	**.0015**
HN on follow-up RBUS	Present	50	12 (24)	20	0 (0)	17	0 (0)	**.005**
Change in HN on RBUS	**Remained**	50	**8 (16)**	20	**0 (0)**	18	**0 (0)**	**.0256**
	Developed		**4 (8)**		**0 (0)**		**0 (0)**	
	Still None		31 (62)		18 (90)		18 (100)	
	Resolved		7 (14)		2 (10)		0 (0)	
VUR on initial VCUG	Yes	51	9 (18)	20	1 (5)	22	3 (14)	.512
Change in VUR, initial to follow up	Remained	18	1 (5.6)	8	0 (0)	8	0 (0)	.626
Bladder wall on follow up	Developed	17	7 (39)	8	4 (50)	8	1 (13)	.141
Change in VUR, initial to follow up	Still none	18	9 (50)	8	4 (50)	8	6 (75)	.626
	Resolved		1 (5.6)		0 (0)		1 (13)	

Note: The bold values indicate significant *p* values.

prenatal repair, while improving the rate of vaginal delivery, reducing the risk of uterine dehiscence, and improving gestational age at delivery.[4] The fetoscopic technique continues to undergo technical modifications aiming to improve maternal outcomes. In our review of our different MMC repairs, we evaluated the prevalence of UDS-based bladder risk categories across pre- and postnatal repair types. The distribution of risk categorization across the various repair types demonstrated a large difference in percentages, albeit not statistically

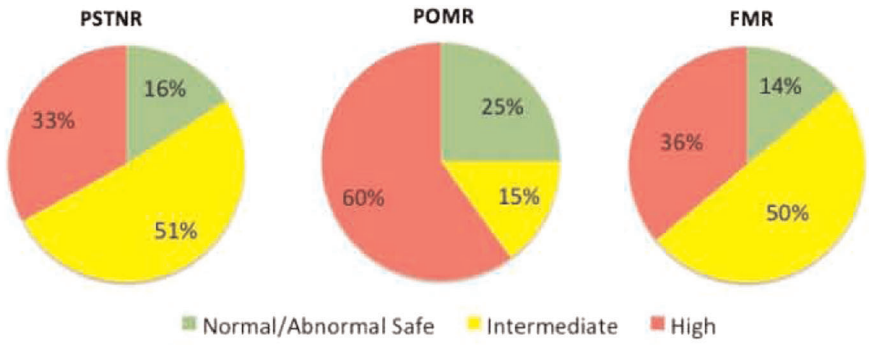

FIGURE 5 This image demonstrates the distribution of each bladder risk category at the time of initial urodynamic study

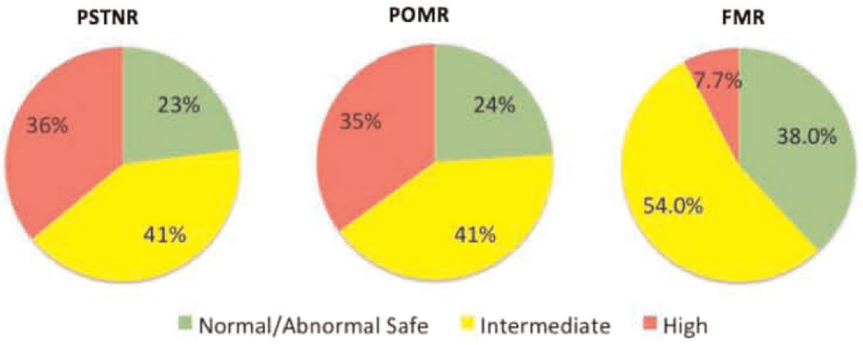

FIGURE 6 This image demonstrates the distribution of each bladder risk category at the time of follow-up urodynamic study

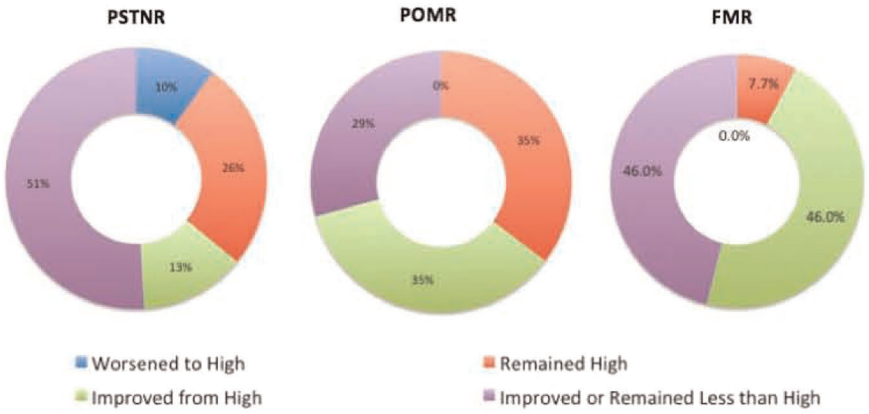

FIGURE 7 This image reviews the bladder risk category changes that occurred between the initial urodynamic study and the follow up urodynamic study

significant, reflecting possible clinical differences in the rates of bladder risk category across the repair types. While there was no statistically significant difference when safe and intermediate-risk groups were combined and compared directly to high-risk categorization, one can quickly see that the overall trend was in favor of the prenatal groups and even more so for the fetoscopic group (60% POMR initial high-risk down to 35% on follow up, FMR declined from 33% to 8%, PSTNR remained stable at 36% with 10% worsening to high-risk from lower risk initially). These data support that fetoscopic repair is, at the very least, comparable to prenatal open repair with a trend suggesting higher prevalence of low-risk bladder categorization. Additionally, these findings are in line with prior studies, which demonstrate a trend towards benefit with prenatal intervention.[15,19]

TABLEE 4 Odds ratio analysis of high-risk bladder on initial UDS and improvement or stability in non-high-risk category at follow up

Odds ratio analysis, high-risk bladder categorization			
Initial UDS high-risk	**Odds ratio**	**Confidence interval**	***p***
PSTNR versus FMR	6.72	0.79 – 57.25	.0814
POMR versus FMR	6.55	0.68-63.33	.1047
Improve from high-risk or remain less than high-risk			
PSTNR versus FMR	0.149	0.02 – 1.27	.0814
POMR versus FMR	0.153	0.02 – 1.48	.1047

On follow up, our results reflect even larger bladder-risk differences across the bladder-repair categories. We found that 10% of the postnatal group worsened to high-risk from previously lower categorization, while none of the prenatally intervened patients worsened, which supports the theory that prolonged exposure of the spinal cord and peripheral nerves to the amniotic fluid results in poorer functioning nerves and thus bladders.[20-23] Other technical factors might well play a role in these findings, including the use of relaxing incision with fetoscopic repair, differences in tissue handling, and the use of minimally invasive techniques. One would expect the novel, recently experimental FMR technique to have diminished outcomes due to the typically steep learning curve associated with new procedures. However, even

TABLE 5 Comparison of prenatal interventions: fetoscopic versus prenatal open

		Fetoscopic		Prenatal open		
Variable name	**Indicator**	**Available *N***	**Count (%)**	**Available *N***	**Count (%)**	***p***
Initial UDS	Normal/abnormal safe	22	3 (14)	20	5 (25)	.055
	Intermediate		11 (50)		3 (15)	
	High		8 (36)		12 (60)	
Initial to follow-up UDS change	**Stayed high**	13	1 (7.7)	17	6 (35)	.24
	Improved from high		6 (46)		6 (35)	
	Same or stayed less than high		6 (46)		5 (29)	
Initial to follow up UDS change (high risk vs. normal/abnormal safe + intermediate)	Improved from high or remained less than high	13	12 (92)	17	11 (65)	.1
HN on initial RBUS	Present	22	0 (0)	20	2 (10)	.13
HN on follow-up RBUS	Present	17	0 (0)	20	0 (0)	
Initial to follow-up change in HN on RBUS	Still none	18	18 (100)	20	18 (90)	.48
	Resolved		0 (0)		2 (10)	

with the learning curve included in our data, FMR trends toward better outcomes based on the reduced percentage of high-risk bladders present. Further studies may further prove or disprove the potential these various factors play in terms of MMC patient outcomes.

We have found that people will travel large geographic distances seeking the latest technologies and care innovations at our specialized, quaternary fetal care center. Our findings support this observation as we found the PSTNR cohort traveled an average of 70 miles from our institution compared to 176 miles for POMR and 362 miles for the FMR population. A limitation that may result from this larger geographic distance traveled by the families is that data capture with longitudinal follow-up may be impacted and less likely than familes and patients staying within their local geographic area and regional healthcare plan. Our follow-up rates per the MMC-intervention groups furthers this notion that the farther one travels for initial intervention, the less likely they are to receive follow up care at the same institution. Accordingly, 24% of PSTNR, 15% of POMR, and 40% of FMR did not have appropriate follow-up studies to analyze (Table 6).

As part of a substudy of the MOMS trial, the MOMS trial investigators are credited with providing what is, to date, largely considered the best data currently available in regard to bladder function between prenatal and postnatal repair.[8] They found no difference in rate of CIC by age 30 months between the prenatal and postnatal repair groups although there was a 13% reduction in CIC rate in favor of the prenatal repair group. In 2019, this same group issued the latest on urologic outcome differences between prenatal and postnatal repair.[15] At issue with this most recent analysis are the outcomes

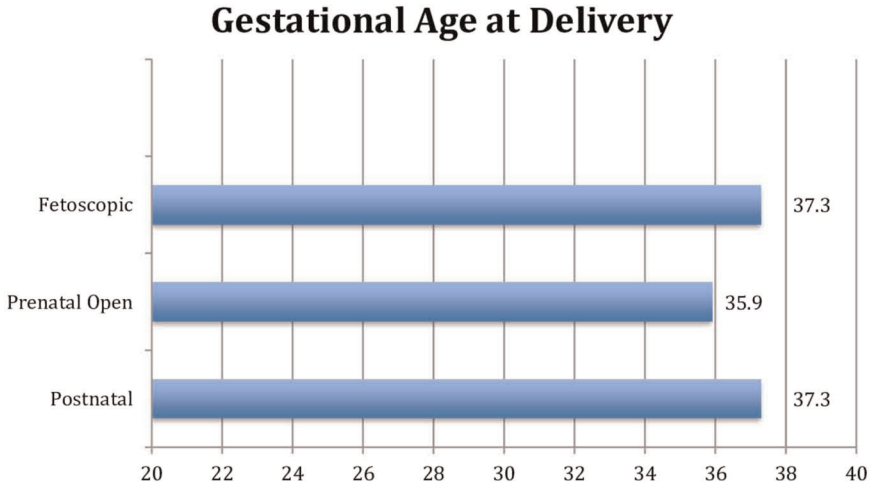

FIGURE 8 This figure details the gestational age at delivery between the three repair types studied

TABLE 6 Follow-up percentage and distance from treating institution

Repair type	Percent with follow-up studies (%)	Average distance from treating institution (miles)
PSTNR	76	71
POMR	85	176
FMR	60	362

Abbreviations: FMR, fetoscopic myelomeningocele repair; POMR, prenatal open in-utero myelomeningocele repair; PSTNR, postnatal repair.

evaluated. When appraised in detail, one can see that this MOMS study failed to provide detailed voiding diaries for those who were identified as volitional voiders. These volitional voiders were simply identified as such by the parent/guardian and a uroflow was subsequently obtained which demonstrated normal voiding pattern in only a very small percentage of these patients. One could surmise that a proportion of those patients prenatally repaired were not performing CIC due to the belief that they had received a superior surgery which should have mitigated the need for CIC and thus would not accept the need for intervention. The necessity for CIC to achieve social continence is, unfortunately for the SB population, almost expected regardless of repair type. It is widely accepted that patients born with spina bifida will rarely have normal innervation of either bladder or sphincter musculature. A small percentage will manage with spontaneous or timed voiding without the need for intervention. The majority of these children will require CIC with or without anticholinergic medications[24] which has been shown to be beneficial in preserving renal function in this population.[25]

SB patients in the low and intermediate-risk group, barring other influencing factors such as high-grade VUR, often do not require clinical interventions to protect the kidneys while those in the high-risk group require immediate intervention upon recognition of this elevated bladder risk. Renal damage and in particular CKD is the primary concern for high-risk bladders. In our experience, prenatal intervention, especially fetoscopic trends towards improved urologic outcomes as can be seen with fewer high-risk bladders both initially and on follow up, regardless of whether CIC or anticholinergic use has been initiated.

There are several other benefits to prenatal repair, as has been demonstrated by prior studies. In fact, the MOMS trial recruitment was stopped early due to the overwhelming benefits including less need for shunts, reduction in hindbrain herniation, improved mental development, and motor function, and an improved ability to walk unaided.[5] Nonetheless, there are significant drawbacks of prenatal repair, which cannot be overlooked or minimalized. The MOMS trial highlighted these issues, including an increased risk of preterm labor and risk of uterine dehiscence. Fortunately, fetoscopic repair greatly mitigates these risks with studies demonstrating improved gestational age, improved rates of successful vaginal deliveries, and decreased rates of scar complications.[26] As can be seen in Figure 7, our study has similar findings with postnatal and fetoscopic repair type having similar gestational age at birth, both of which are greater than that seen with prenatal open repair.

Embracing the fact that CIC is almost universal in SB will allow providers to see this intervention as minimal in the grand scheme of things, as ensuring the upper tracts are safe is the most important outcome. The authors' belief is that fetoscopic repair is comparable to prenatal open repair and may, in fact, result in a lower prevalence of high-risk bladders later in life, with or without CIC and/or anticholinergics, given the findings of notable percentage differences between the groups. The fact that CIC is required for social continence should not be the primary or final outcome, rather, long-term data should focus on the establishment or attainment of safe, "non-hostile" bladders and reducing the need for augmentation surgery and reducing the risk of CKD and renal failure. Given the trend seen in bladder risk improvement with prenatal intervention, and especially fetoscopic repair, it seems reasonable that long-term studies might support the hypothesis that augmentation rates will decline and the possibility of lower risk of CKD will result with fetoscopic MMC repairs.

5 | LIMITATIONS

Our study is not without limitations, which the authors recognize as inevitable given the retrospective nature of the study. Similar to other studies within SB, the small cohort sizes limit the ability of the data to reach statistical significance. Additionally, fetoscopic repair remains an ever-evolving intervention with constantly improving outcomes. Improvements in surgical technique for fetoscopic repair differ from the other repair types, which might ultimately prove to be responsible for improved outcomes with FMR. Relaxing incisions, use of minimally invasive techniques, and differences in tissue handling all might well play a significant role in outcomes.

As previously noted, a large number of patients did not have follow-up studies in each cohort with the largest percentage failing to follow up in the FMR cohort. Certain data points were felt to not be applicable given the

inherent constraints present due to some patients traveling long distances disallowing tight control of study timing. The authors provided all available data as best it could without breaking the data down into unusably small cohorts, which would be underpowered for interpretation. The authors nevertheless felt it was important to have a snapshot of how these bladders are behaving in the first year of life, regardless of whether progression can be tracked.

Another potential criticism is the simplistic, binary outcomes we used for reporting our imaging outcomes. We acknowledge that we did not utilize specific HN grades as there is a lack of uniform agreement of HN grading systems amongst radiologists and likewise, we did not stratify grades of VUR as there can be interobserver variability. Using our binary approach for the presence or not of HN or VUR was felt to offer less confounded data variability and ultimately provide a more critical reflection of our study cohorts.

Despite all patients meeting the MOMS criteria, there is heterogeneity of the level of the MMC lesions that were repaired. Lesion levels were evaluated with bladder-risk categorization and the percentage of high-risk categorization within thoracic, lumbar, and sacral levels all ranged from 38% to 60% (Table 2, Figures 3 and 4). The small cohort sizes (nine thoracic, five sacral) subsequently did not allow appropriate power for analysis.

Our study population does include a large percentage of Hispanic patients, which is different from most institutions in the United States with large SB populations. While we know that more Hispanic patients undergo postnatal repair versus prenatal repairs, we cannot comment on Hispanic heritage being associated with different outcomes if repair type is controlled.

Additionally, heterogeneity in management amongst SB care providers is present at our institution and across the globe. As a quaternary care center, patients can be managed at outside institutions thus limiting our institution's ability to standardize the care of these patients. While this heterogeneity could alter management, it was assumed that management intervention would be equally dispersed and applied no differently between the groups.

6 | CONCLUSIONS

Prenatal repair appears similar to postnatal open intervention in terms of rates of high-risk bladder categorization. Fetoscopic repair of MMC shows promising results with less prevalence of high-risk bladders on baseline and short-term follow-up and warrants continued evaluation as this urological benefit may reduce the risk potential for CKD. This reduction of CKD may further result in significant public health implications that are comparable to neurological benefits with reduction of VP shunts in prenatally repaired MMC patients.

CONFLICT OF INTERESTS

Paul F. Austin is a Consultant for Allergan and Urovant. The other authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Gerber JA, Stocks BT, Zhu H, et al. Prevalence of high-risk bladder categorization with prenatal and postnatal myelomeningocele repair types. *Neurourol Urodyn*. 2021;1–11. https://doi.org/10.1002/nau.24629