

In Utero Closure of Myelomeningocele Does Not Improve Lower Urinary Tract Function

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Purpose: Recent data comparing prenatal to postnatal closure of myelomeningocele showed a decreased need for ventriculoperitoneal shunting and improved lower extremity motor outcomes in patients who underwent closure prenatally. A total of 11 children whose spinal defect was closed in utero were followed at our spina bifida center. We hypothesized that in utero repair of myelomeningocele improves lower urinary tract function compared to postnatal repair.

Materials and Methods: Eleven patients who underwent in utero repair were matched to 22 control patients who underwent postnatal repair according to age, gender and level of spinal defect. Urological outcomes were retrospectively reviewed including urodynamic study data, need for clean intermittent catheterization, use of anticholinergic agents and prophylactic antibiotics, and surgical history. The need for ventriculoperitoneal shunting or spinal cord untethering surgery was also reviewed.

Results: Mean followup was 7.2 years for patients who underwent in utero repair and 7.3 years for those who underwent postnatal repair. Mean patient age at compared urodynamic studies was 5.9 years for in utero repair and 6.0 years for postnatal repair. The in utero repair group was comprised of 5 lumbar and 6 sacral level defects with equal matching (1:2) in the postnatal repair cohort. There were no differences between the groups in terms of need for clean intermittent catheterization, incontinence between catheterizations or anticholinergic/antibiotic use. Urodynamic parameters including bladder capacity, detrusor pressure at capacity, detrusor overactivity and the presence of detrusor sphincter dyssynergia were not significantly different between the groups. There was no difference in the rate of ventriculoperitoneal shunting ($p = 0.14$) or untethering surgery ($p = 0.99$).

Conclusions: While in utero closure of myelomeningocele has been shown to decrease rates of ventriculoperitoneal shunting and improve motor function, it is not associated with any significant improvement in lower urinary tract function compared to repair after birth.

Key Words: meningomyelocele; urinary bladder, neurogenic

SPINA bifida is a disorder of incomplete embryonic neural tube closure occurring in approximately 1 of every 1,000 live births.¹ MMC is the most common form of spina bifida, characterized by extrusion of the spinal cord into a sac filled with cerebrospinal

fluid.² Although MMC is a treatable central nervous system abnormality, it incurs varying degrees of damage to the spinal cord leading to significant morbidity such as spine deformity, lower extremity distortion and paralysis, and bowel/bladder dysfunction.

Abbreviations and Acronyms

CIC = clean intermittent catheterization
DSD = detrusor sphincter dyssynergia
EMG = electromyography
IUR = in utero repair
LUT = lower urinary tract
MMC = myelomeningocele
MUP = motor unit potentials
PNR = postnatal repair
UDS = urodynamic studies
UR = ureteral reimplantation
US = ultrasonography
VPS = ventriculoperitoneal shunting
VUR = vesicoureteral reflux

Study received institutional review board approval.

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Until the 1970s MMC was fatal in the majority of infants, but improved medical and surgical care has resulted in children living well into adolescence and adulthood. In addition, prenatal detection has helped with family counseling and preparation for postnatal intervention.

Due to advances in fetal surgery and prenatal anesthesia, in utero neural tube defect closure has become an option for the treatment of MMC. This procedure has been performed in a randomized prospective fashion at 3 American centers as part of the National Institutes of Health sponsored clinical trial, MOMS (Management of Myelomeningocele Study).³ Limited data from the 1980s and 1990s derived from case reports or small case series initially supported the hypothesis that the prenatal closure of MMC was superior to traditional postnatal closure with regard to fetal outcomes related to MMC. More recently the first published data from the MOMS trial demonstrated a reduction in need for VPS and improved lower extremity motor outcomes.⁴ However, the urological outcomes from this multi-institutional study have not yet been reported. At our institution we treated 13 children in the MOMS trial, and with the relocation of 2 patients we have complete data on 11. We hypothesized that LUT function would be improved in patients who underwent IUR vs PNR.

MATERIALS AND METHODS

After obtaining institutional review board approval we retrospectively reviewed 11 children who underwent IUR elsewhere and were referred to our institution for postnatal care since 1999. These children were matched to 22 children who underwent PNR in terms of age, gender and level of the spinal lesion. These controls were chosen blindly from our database of patients with MMC to minimize selection bias. These children were followed at our spina bifida center and underwent regular algorithmic followup, which includes renal/bladder US, voiding cystourethrography if indicated and urodynamic evaluation.

At our institution UDS includes cystometrography and needle urethral sphincter EMG with neurological evaluation by a neurologist. Cystometry is performed via a 7Fr triple lumen catheter using saline warmed to 37C at an infusion rate of 10% of estimated or known bladder capacity. Bladder capacity and contractility, maximum bladder and leak point pressure, and presence or absence of detrusor overactivity were recorded on a multichannel urodynamic recorder (Triton®). Simultaneous EMG was obtained by placing a 24 gauge concentric needle electrode, perineally in boys and paraurethrally in girls, which was advanced into the external urethral sphincter muscle. Bioelectrical activity was observed on an oscilloscope, heard on the audio channel and recorded on an EMG amplifier (TECA™ Synergy T2X). Individual MUP at rest in response to various sacral reflexes and bladder filling and emptying were assessed to gauge the degree of denervation. DSD was noted when there was no reduction or an

increase in sphincter activity when bladder filling reached capacity and leakage occurred, or during a voiding contraction.

UDS data were collected at various points in patient postnatal care. To make valid comparisons we evaluated UDS data from the 2 groups with patients at similar ages. All matched studies from the 2 cohorts were performed within 1 year of each other except for 2 cases in which the studies were performed 18 and 24 months apart. The most recent UDS data that were amenable to being matched according to patient age were included in the study. In addition, comparisons were made before any major surgical intervention was performed to allow for consistent assessment and to exclude confounding factors that could alter bladder dynamics. Additional data evaluated included need for CIC, urinary continence status, use of anticholinergic agents and antibiotic prophylaxis, and need for major urological surgery. Secondary outcomes included need for VPS and spinal cord untethering surgery. Student's t test or Fisher's exact test was used to compare cases to controls based on data characteristics. Statistical testing was performed with SAS® 9.2 and a 2-sided $p < 0.05$ was considered significant.

RESULTS

Of the 33 patients evaluated there were 5 boys and 6 girls in the IUR group, and 10 boys and 12 girls in the PNR group. Five lumbar and 6 sacral level defects comprised the IUR group with equal matching (1:2) in the PNR group. For the IUR group the mean age at which patients first presented to our spina bifida center to establish care was 18.7 months (range 1 month to 6 years). Mean patient age at first UDS was 20 months for the IUR group and 15 months for the PNR group. All patients have been seen in followup in the last year as of this writing except for 2 in the PNR group who were last seen 2 and 2.5 years ago (see table).

In terms of urological outcomes 8 of 11 (73%) patients who underwent IUR currently require CIC vs 18 of 22 (82%) in the PNR group ($p = 0.66$). Of the 8 patients in the IUR group who perform CIC 4 entered the program performing CIC and 2 others were started on CIC at the first visit. Indications for CIC included the presence of DSD, poorly compliant bladder and increased post-void residual. Not all patients with DSD were instructed in CIC, including those with low detrusor pressure and adequate bladder emptying at low pressure. Of those who require CIC 5 of 8 (63%) in the IUR group had incontinence between catheterizations vs 15 of 18 (83%) in the PNR group ($p = 0.33$). Use of anticholinergic agents and antibiotic prophylaxis was similar between the 2 cohorts. Urodynamic parameters including bladder capacity, detrusor overactivity, maximum pressure at capacity and leakage on UDS were not sta-

Comparison of prenatal vs postnatal closure of MMC

	Prenatal Closure	Postnatal Closure	p Value
Mean \pm SD yrs followup	7.2 \pm 4.2	7.3 \pm 4.2	0.96
Mean \pm SD age at compared UDS	5.9 \pm 4.3	6.0 \pm 4.2	0.93
No./total No. need for CIC (%)	8/11 (73)	18/22 (82)	0.66
No./total No. incontinence between CIC (%)	5/8 (63)	15/18 (83)	0.33
No./total No. need for anticholinergic agents (%)	8/11 (73)	16/22 (73)	0.99
No./total No. need for antibiotic prophylaxis (%)	3/11 (27)	6/22 (27)	0.99
No./total No. need for bowel regimen (%)	7/11 (64)	8/22 (36)	0.16
No./total No. VPS (%)	3/11 (27)	13/22 (59)	0.14
No./total No. untethering surgery (%)	3/11 (27)	6/22 (27)	0.99
Mean \pm SD ml capacity	241 \pm 160	241 \pm 143	0.99
Mean \pm SD cm H ₂ O detrusor pressure at capacity	22 \pm 17	22 \pm 16	0.97
No./total No. detrusor overactivity (%)	3/11 (27)	7/22 (32)	0.99
No./total No. leakage on UDS (%)	4/11 (36)	15/22 (68)	0.14
No./total No. DSD (%)	6/8 (75)	18/19 (95)	0.20

tistically different between the groups (see table). Of the 11 patients who underwent IUR 2 (18%) had decreased bladder capacity as did 5 of the 22 (23%) who underwent PNR.

Comparison of sphincter EMG data demonstrated that there was no difference in the rate of DSD between the groups ($p = 0.20$). In the IUR group 6 of 11 (55%) patients had severe sphincter denervation (fibrillation potentials) on EMG but 4 of these 6 (67%) demonstrated re-innervation (polyphasic MUP) of the sphincter with persistent DSD on the most recent EMG. The mean time at which patients in the IUR group were found to have sphincter re-innervation was 2.8 years. The other 2 patients who underwent IUR with denervation initially had normal MUP (with or without DSD) but deteriorated to severe denervation at a mean of 3.5 years. Two (18%) other patients who underwent IUR had partial sphincter denervation which remained stable throughout followup. The other 3 children in the IUR group (27%) had normal MUP on all EMG studies. Of these patients 2 were synergic and 1 had DSD.

In the PNR group 10 of 22 patients (46%) demonstrated severe denervation on EMG. Of these 10 patients 8 were found to have severe denervation on initial EMG but 2 of the 10 had initial normal MUP that deteriorated to denervation during a 5-year period. Of the 10 children with sphincter denervation 5 had re-innervation on the last EMG with a mean time to re-innervation of 3.8 years. In the PNR group 9 children (41%) demonstrated partial denervation on EMG and of these patients 2 initially had normal MUP with DSD that progressed to partial

denervation at a mean followup of 3 years. Two patients who underwent PNR (9%) had normal MUP with DSD and 1 (5%) had a normal EMG without DSD. One other patient who underwent PNR (5%) who recently established care at our institution was awaiting initial EMG evaluation.

On the first visit for patients in the IUR group, upper tract findings did not differ between those who performed CIC and those who did not (1 had hydronephrosis and did not perform CIC, and 3 had hydronephrosis with or without VUR and did perform CIC). Two patients who underwent IUR had VUR on initial examination (1 underwent UR and 1 had spontaneous resolution). On last radiological evaluation 2 (18%) patients in the IUR group had new onset unilateral moderate to high grade VUR on voiding cystourethrography or radionuclide cystography with associated hydronephrosis on US. In the PNR group 5 (23%) patients had a history of moderate grade VUR but all reflux spontaneously resolved at last clinic followup. Of these patients 4 had normal US results at last followup, and 1 had evidence of renal scarring and size discrepancy compared to the unaffected side. The other 17 patients in the PNR group had normal US results.

Two of 11 (18%) patients from the IUR group and 5 of 22 (23%) from the PNR group required major urological surgery related to pathological bladder function (see Appendix). The difference in VPS rate for the 2 groups did not reach statistical significance ($p = 0.14$). The rate of spinal cord untethering surgery was equal.

DISCUSSION

MMC is a serious and common form of spina bifida in which an unfused portion of the vertebral column allows caudal protrusion of the meninges and spinal cord. The consequences of this process are variable, depending on the level of the spinal cord abnormality, with higher level defects associated with more severe nerve dysfunction and paralysis.⁵ Traditional treatment involves closure of the spinal defect during the first few days of life. A majority of infants will also require VPS to treat hydrocephalus. More recently fetal surgery has been performed to close MMC defects in hopes of limiting the damage sustained by the spinal cord.

The MOMS trial was started in 2003 to evaluate the safety and efficacy of in utero surgery for MMC. The trial closed in 2010 with the conclusion that IUR resulted in a decreased need for VPS, reversal of the hindbrain herniation component of the Chiari II malformation, and reduced the incidence or severity of motor function impairment.⁴ Urological outcomes were not reported in this trial. However, several retrospective studies have been conducted to evaluate

the LUT function of patients with prenatally closed MMC. In separate studies the urodynamic findings in patients who underwent IUR have been comparable to those previously reported in the literature for patients with MMC who underwent PNR.^{6,7}

Koh et al were the first to compare the 2 groups.⁸ In their study 5 patients who underwent IUR were compared to 88 children who underwent PNR who had similar level lesions. They reported that those who underwent IUR had complete denervation of the external sphincter on EMG, whereas only 39% of the postnatal cohort had denervation on newborn evaluation, with similar findings on 1-year evaluation. In addition, 100% of the IUR cases had detrusor overactivity on UDS compared to 38% of the PNR cases at newborn evaluation, and the findings at 1 year were again similar. These 5 patients who underwent IUR were included in the present study along with 6 others followed at our institution since that publication. In this study we evaluated longer term outcomes of these patients with MMC who underwent prenatal closure with a mean followup of 7 years. Whereas Koh et al matched children who underwent IUR with newborns who had similar neurological levels, we matched patients according to age, gender and spinal level to allow for more precise and valid comparison and assessment. Interestingly, 4 of the 5 patients who underwent IUR who were originally reported by Koh et al demonstrated re-innervation to the external sphincter on subsequent UDS. Therefore, it is hoped that although patients who underwent IUR may have initial deterioration of LUT function, it may spontaneously improve and equilibrate over time. This ability to re-innervate the external urethral sphincter also seems to apply to postnatally repaired MMC as 5 of 10 these patients with denervation had similar re-innervation.

The benefits of performing fetal closure of MMC must be weighed against the risks. Adzick et al reported more pregnancy complications among women in the prenatal surgery group including oligohydramnios, chorioamniotic separation, placental abruption and spontaneous membrane rupture.⁴ In addition, those treated prenatally were born with higher rates of prematurity, which is likely the reason this subset had more cases of respiratory distress syndrome. However, the benefits of fetal closure as reported by the MOMS trial include a reduced need for VPS at age 12 months and improved motor outcomes at age 30 months. It will be interesting to see if these improved neurological parameters are durable in a longer followup period. In this study we were unable to demonstrate improved urological function between the 2 groups at a mean followup of 7 years, and fetal intervention for MMC may not attenuate LUT dysfunction as we hypothesized. In addition, we did not appreciate a lower rate of

VPS. Our findings may suggest that caution should be taken in broadly adapting this novel therapy compared to traditional approaches as the risks are not inconsequential and the outcomes may not be superior in various aspects of the disease process. It would be interesting to determine if orthopedic and neuropsychological outcomes are improved in fetally closed MMC as these have not been reported to date to our knowledge.

Our study has several limitations. Our sample size was limited due to the number of patients who underwent IUR who were followed at our institution. Because we do not perform in utero MMC closure at our institution, we were only able to evaluate children who lived in or moved to the referral area and sought evaluation at our institution. Therefore, our small sample size may not represent the true population of patients treated with IUR. This is likely why we were unable to obtain statistical significance with the VPS rate between the 2 groups, although the percentages do appear to be different (IUR group 27% vs PNR group 59%). In addition, we attempted to eliminate the selection bias with our control patients by blindly choosing controls, but recognize that this method may not allow us to represent the average patient who underwent PNR. In addition, due to the influx of patients with MMC to our institution at various points (from birth to several years old) in the IUR and PNR populations, it was difficult to make assessments with data missing from prior care elsewhere. Each patient also had different evaluation schedules based on the severity of the disease process with more affected individuals having more frequent followup. A prospective evaluation would provide more meaningful results. We await forthcoming data from the MOMS trial to more fully address urological outcomes after fetal closure. As with all patients with MMC who underwent postnatal closure, early, sequential and close urological evaluation with radiography and UDS is important for children with fetal closure to prevent upper tract deterioration.

CONCLUSIONS

Although the MOMS trial demonstrated a reduced need for VPS and improved motor outcomes, patients with fetal closure of MMC appear to have lower urinary tract function equivalent to those who underwent postnatal closure. However, given our small sample size and possible confounding factors, we await the results of larger scale randomized prospective trials. These findings underscore the importance of close monitoring of the urinary tract with urodynamic evaluation and radiological imaging in the immediate postnatal period as well as in the long term.

APPENDIX

Major Urological Surgeries for the 2 Cohorts

IUR Cohort	PNR Cohort
1 Bilateral UR for VUR due to recurrent febrile urinary tract infections	1 Intravesical botulinum toxin injections
2 Creation of Monti continent catheterizable stoma, Malone antegrade continence enema, bladder augmentation, unilateral UR	2 Bladder augmentation and bilateral UR
3 Scheduled for artificial urinary sphincter placement	3 Creation of Malone antegrade continence enema, artificial urinary sphincter placement, later bladder augmentation and creation of Monti catheterizable stoma
	4 Artificial urinary sphincter placement
	5 Unilateral UR
	6 Scheduled for creation of continent catheterizable stoma
	7 Scheduled for creation of continent catheterizable stoma

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