Title
Orthopaedic outcomes of prenatal versus postnatal repair of myelomeningocele

Journal
Journal of Pediatric Orthopaedics B, 31(1)

ISSN
1060-152X

Authors
Swarup, Ishaan
Talwar, Divya
Howell, Lori J
et al.

Publication Date
2022

DOI
10.1097/bpb.0000000000000827

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr Orthop B. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

J Pediatr Orthop B. 2022 January 01; 31(1): 87–92. doi:10.1097/BPB.0000000000000827.

Orthopaedic outcomes of prenatal versus postnatal repair of myelomeningocele

Ishaan Swarup[a], **Divya Talwar**[b], **Lori J. Howell**[c], **N. Scott Adzick**[c], **Bernard David Horn**[b]

[a]Division of Pediatric Orthopaedic Surgery, University of California San Francisco, UCSF Benioff Children's Hospital Oakland, Oakland, California

[b]Division of Orthopaedics, Children's Hospital of Philadelphia, 3401 Civic Center Boulevard

[c]Division of Pediatric General, Thoracic, and Fetal Surgery, Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, Pennsylvania, USA

Abstract

Background: Myelomeningocele is the most common form of spina bifida and is characterized by extrusion of the spinal cord through a spinal canal defect. It often results in lifelong disability and significant orthopaedic issues such as spinal deformity, hip abnormalities, and clubfoot. A randomized controlled trial has shown efficacy of prenatal repair in decreasing the need for shunting and improving motor outcomes. However, no studies have evaluated the effects of prenatal repair on orthopaedic outcomes. The purpose of this study was to determine the rates of orthopaedic conditions in patients with prenatal and postnatal repair of myelomeningocele, as well as compare the rates of treatment required for orthopaedic conditions.

Methods: This study analyzes the relevant outcomes from a prospective randomized controlled trial (Management of Myelomeningocele Study, MOMS). Eligible women were randomized to prenatal or postnatal repair, and patients were evaluated prospectively. Outcomes of interest included rates of scoliosis, kyphosis, hip abnormality, clubfoot, tibial torsion, and leg length discrepancy at 12 months and 30 months. Additionally, we evaluated the need for orthopaedic intervention, notably casting and bracing at the same time points. Statistical analyses included descriptive statistics and univariate analyses.

Results: The data for the full cohort of 183 patients was analyzed (91 prenatal, 92 postnatal). Patient demographics have been previously described by the MOMS investigators. There were no differences in the rates of scoliosis, kyphosis, hip abnormality, clubfoot or tibial torsion between patients treated with prenatal or postnatal repair. However, the rate of leg length discrepancy was lower in the prenatal repair group at 12 months and 30 months (7% vs. 16% at 30 months, $p = 0.047$). In addition, the rates of patients requiring casting or bracing was significantly lower in patients treated with prenatal repair at 12 months and 30 months (78% vs. 90% at 30 months, $p = 0.036$).

Conclusion: Patients that are treated with prenatal repair of myelomeningocele may develop milder forms of orthopaedic conditions and may not require extensive orthopaedic management.

Correspondence to Bernard David Horn, MD, Division of Orthopaedics, Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA Tel: +215 590 1527; hornd@email.chop.edu.

Keywords

myelomeningocele; prenatal repair; postnatal repair; orthopaedic outcomes; fetal surgery

INTRODUCTION

Spina bifida is the most common congenital anomaly of the central nervous system that is compatible with life, and myelomeningocele (MMC) is the most frequent form of this condition[1]. MMC is characterized by extrusion of the spinal cord without any overlying dura, bone, muscle or skin[1]. Its incidence is approximately 3.4 per 10,000 live births in the United States despite folic acid fortification[2]. Patients with MMC often have lifelong disabilities, and it is associated with neural pathology such as Arnold-Chiari II malformation and hydrocephalus. The neural elements become damaged from exposure to the toxic effects of amniotic fluid leading to associated long-term morbidity and mortality. Cerebrospinal fluid (CSF) leaks out through the MMC and as a consequence the hindbrain herniates into the cervical spinal canal and obstructs CSF circulation leading to hydrocephalus and brain damage. Orthopaedic issues in these patients include rotational disorders, hip dislocation, joint contractures, foot deformity, fractures, and spinal deformity including scoliosis and kyphosis [3, 4]. Management of orthopaedic conditions is contingent upon the level of disease. Nonoperative treatments include bracing and orthotics[5, 6], and severe cases in higher functioning patients may be addressed with surgical management[7, 8].

Myelomeningoceles are usually detected in utero, and traditional management was comprised of postnatal repair[9]. Techniques for prenatal repair of MMC were developed to decrease the risk of in utero spinal cord injury, and preliminary studies showed more desirable outcomes but associated maternal and fetal risks[1, 9]. More recently, a prospective randomized controlled trial by Adzick et al. conclusively showed that prenatal repair was associated with the reduced need for cerebrospinal fluid shunting, decreased incidence of hindbrain herniation, and improved motor outcomes at 30 months compared to postnatal repair[1]. This study was called the Management of Myelomeningocele Study (MOMS), and evaluation of additional data has validated improvements in mental development, motor function, ambulation, and self-care[9, 10]. However, the orthopaedic and musculoskeletal outcomes from this study have not been evaluated.

The purpose of this study was to determine the prevalence of orthopaedic conditions in patients with prenatal and postnatal repair of MMC, as well as compare the rates of treatment required for orthopaedic conditions. We hypothesized that the prevalence of orthopaedic conditions and need for orthopaedic management would be lower in patients undergoing prenatal repair.

METHODS

Study Design

MOMS was conducted at three major fetal surgery centers, specifically Children’s Hospital of Philadelphia, University of California San Francisco, and Vanderbilt University. An

independent data coordinating center was established at the George Washington University Biostatistics Center. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) provided funding and oversight. This trial received approval from the institutional review board (IRB) at each study center.

Eligible patients included women carrying a fetus with MMC diagnosed between 19–25 weeks of gestation, maternal age 18 years or older, lesion level T1 – S1, evidence of hindbrain herniation, and normal karyotype. Patients with any other fetal anomaly unrelated to MMC, severe kyphosis, risk for preterm birth, placental abruption, body-mass index ≥ 35, and contraindication to surgery were excluded. Patients that were randomized to prenatal repair underwent hysterotomy and MMC repair, and patients randomized to postnatal repair underwent delivery via caesarian section at 37 weeks followed by MMC repair. Children in this study returned to the centers at 12 months and 30 months of age for physical and neurological examination, as well as developmental testing. Patients that were unable to return to their center received home visits. The details of this prospective, randomized controlled trial have been previously published (clinicaltrials.gov, ID NCT00060606) [1].

Outcomes of Interest

The study had two primary outcomes. The first was a composite of fetal/neonatal death or the need for a CSF shunt defined as either placement of a shunt or meeting objective criteria for shunt placement at 12 months of age. Composite score of the Mental Development Index of the Bayley Scales of Infant Development II and the motor function adjusted for anatomic lesion level at 30 months of age was the second primary outcome. Maternal, fetal, and neonatal surgical and pregnancy outcomes were reported as secondary outcomes. Orthopaedic outcomes of interest included scoliosis, kyphosis, hip abnormality, clubfoot, tibial torsion, and leg length difference. Plain radiographs, ultrasound, and magnetic resonance imaging were used to confirm the presence of orthopaedic conditions, and it was confirmed by independent evaluation by trained orthopaedic surgeons and pediatricians at 12 months and 30 months. The presence of hip abnormality was assessed at the first neonatal exam (baseline), and the presence of clubfoot was assessed at the screening ultrasound and first neonatal exam baseline. Additionally, another outcome of interest included treatment for orthopaedic conditions with casts, wraps, braces, or positioners at the 12 month and 30 month time points, which was recorded by independent evaluators at follow-up visits.

Statistical Analysis

Descriptive statistics continuous data were calculated as means and standard deviations whereas frequencies and percentages were calculated for categorical variables. Comparisons between groups were analyzed by using Wilcoxon test for continuous data and Chi-square or Fischer exact tests for categorical data. Relative risk with 95% confidence interval was calculated using exact methods where appropriate. A multivariate logistic regression of the prenatal surgery group was developed adjusting for baseline characteristics. Two-tailed values of $p < 0.05$ were considered statistically significant. The multivariable model included adjustment for hip abnormality, treatment procedure and leg length discrepancy at 12 and 30 month.

RESULTS

Baseline Characteristics

The intended enrollment of MOMS was 200 patients, but recruitment was terminated after 183 patients due to the efficacy of prenatal surgery. Specifically, 91 patients were randomized to prenatal repair and 92 patients were randomized to postnatal repair (Figure 1). There were no significant differences in most baseline characteristics including gestational age at randomization, race/ethnicity, education level, body mass index, smoking status, and presence of clubfoot on prenatal ultrasound (26.4% in prenatal repair group vs. 20.7% in postnatal repair group) ($p > 0.05$). There were significant baseline differences in sex and lesion level between groups. In particular, there were more female fetuses in the postnantal repair group (62% in postnantal reappear group vs. 46.2% in prenatal repair group, $p = 0.03$), and patients in the prenatal repair group had a higher lesion level ($p = 0.02$, Table 1A). Additional demographic details have been previously reported[1, 9, 10].

Orthopaedic Outcomes

There were several orthopaedic conditions that affected patients with MMC at baseline (Table 1A). The most common orthopaedic condition noted in patients with MMC was a hip abnormality (25.4%), clubfoot (23.5%), and scoliosis (14.4%). In comparing between groups, patients that underwent prenatal surgery had a lower rate of leg length discrepancy at 12 months and 30 months ($p < 0.05$). There were no other differences in the prevalence of orthopaedic conditions between groups (Table 2); however, data on each condition was not available for all patients. In the multivariate analysis controlling for baseline factors, there was a lower risk of leg length discrepancy at 12 months (OR = 0.17, $p = 0.03$), and a trend towards a lower risk at 30 months (OR = 0.42, $p = 0.08$, Table 3).

In total, 40 patients underwent orthopaedic surgery over the course of the study period. In the prenatal surgery group, 19 patients underwent any orthopaedic surgery while 21 patients in the postnatal surgery group underwent any orthopaedic surgery ($p > 0.05$). In comparison, significantly fewer patients in the prenatal repair group needed treatment with casts, wraps, braces, or positioners at 12 months (37.7% vs. 53.9%) and 30 months (78.2% vs. 89.8%) in the multivariate regression model controlling for baseline characteristics ($p < 0.05$, Figure 2).

DISCUSSION

Patients with MMC are affected by several orthopaedic conditions, which are associated with significant morbidity and in some cases, mortality. MOMS has conclusively shown the benefits of prenatal repair of MMC. Specifically, prenatal repair has been shown to decrease the risk of death and need for CSF shunting[1], as well as improvement in mental development, motor development, independent ambulation, ability to self-care, and a functional level of spinal cord functioning at least 2 better than the anatomic level of MMC[9]. In this study, we found that the prevalence of leg length discrepancy is six-times lower at 12 months and almost half at 30 months in patients that underwent prenatal repair compared to postnatal repair. The prevalence of other major orthopaedic conditions

is similar between both groups. Additionally, the need for nonoperative orthopaedic management is decreased by approximately 30% at 12 months and 13% at 30 months in patients that undergo prenatal repair.

There may be several factors associated with decreased rates of leg length discrepancy in patients that underwent prenatal repair for MMC. Leg length discrepancy in patients with MMC may be due to hip dislocation, flexion contractures, atypical skeletal development, and physeal fractures[8, 11–13]. Patients that undergo prenatal repair are noted to have better motor development and ability to ambulate[9], which may results in lower risks of flexion contractures and fractures due to disuse osteoporosis. While the rates of hip abnormality recorded at birth were higher in the prenatal surgery cohort, this finding did not reach statistical significance. Additionally, this study did not collect follow-up data on hip abnormalities, and we are unable to comment on the role of hip dislocation on leg length discrepancy. However, in the multivariate analysis controlling for hip abnormality, the prevalence of leg length discrepancy continued to remain lower at 12 months.

It is clear that patients that undergo prenatal repair of MMC need fewer orthopaedic interventions than those who have postnatal repair of their defects. These patients are more functional and independent as shown in previous studies, and function at higher levels than would be predicted by their anatomic level of disease [9]. As a result, they have a lower need for casting, bracing, and positioners. However, patients that undergo prenatal or postnatal repair have high and similar rates of scoliosis and kyphosis, which may require bracing in early disease. Similarly, the rates of clubfoot are similar at baseline, which likely require equal rates of casting and bracing for management. It is possible that the lower rates of orthopaedic interventions in patients with prenatal repair may be due to less severe disease, which may require less intervention despite similar prevalence of each condition. The rates of operative management of orthopaedic conditions was similar in both groups, but we are unable to compare the treatments further due to lack of surgical data in this study.

This study has several implications to orthopaedic surgeons. Patient referrals to orthopaedic surgery for consultation after in utero diagnosis of MMC are common, and it is important for orthopaedic surgeons to offer appropriate counseling. The results of this study show that patients that undergo prenatal repair may have a lower prevalence of leg length discrepancy, and typically require fewer orthopaedic interventions in the first 30 months of life. It is important to note that these results were noted despite patients in the prenatal repair group at the time of initial prenatal evaluation having more severe lesions than patients in the postnatal repair group. It is possible that the orthopaedic benefits of prenatal repair may be even more significant in patients with lower level lesions that have better lower extremity function. However, these benefits should be weighed against the risks of prematurity and maternal morbidity. In general, orthopaedic surgeons should refer patients to specialized pediatric centers for evaluation if appropriate. This practice will allow patients to make better informed decisions for themselves and their fetus, as well as potentially improve long-term outcomes for children with MMC.

This study has several strengths. First, this study is a randomized controlled trial, which provides the highest level of evidence on determining the efficacy of prenatal repair, and it

is the only study to our knowledge to assess orthopaedic outcomes after prenatal repair of MMC. Second, the data from this study was obtained by blinded practitioners and stored at an independent center thereby decreasing the risk of bias. Third, the study was performed at three centers across the United States, which improves the generalizability of the findings of this study.

On the other hand, this study has several limitations. There is limited orthopaedic data as well as general functional and developmental data available in this study. All data points collected were determined at the outset of the study and are general in nature. The data are not more detailed with regards to specific etiologies and pathology that account for many of the findings such as leg length difference or hip pathology. It is well-known that patients with MMC have various orthopaedic conditions, and based on the available data, we are only able to study the effects of prenatal repair on prevalence and nonoperative management of these conditions. Similarly, the study may be underpowered to assess certain orthopaedic outcomes, since it was powered according to its primary outcomes of interest. Lastly, there is limited radiographic or surgical data for review, and there is only baseline data on conditions such as hip abnormality and clubfoot. Additionally, indications for management may be subjective and influence overall rates of management. Even though MOMS underwent rigorous data collection and analysis, future prospective studies with larger cohorts may provide additional data regarding orthopaedic conditions and management.

In conclusion, MMC is associated with several orthopaedic conditions. Prenatal repair of MMC has been shown to decrease the risk of death and need for CSF shunting and to improve lower extremity motor function, and from an orthopaedic perspective, it is associated with a lower prevalence of leg length discrepancy and need for nonoperative orthopaedic management. In general, it is possible that patients that undergo prenatal repair may present with milder forms of orthopaedic conditions, and may not require extensive orthopaedic management. Prenatal repair of MMC should be considered in appropriate cases, and patients should be referred to specific centers for additional counseling and management.

Acknowledgments

Source of Funding

The original study was funded by the National Institutes of Health (ClinicalTrials.gov number, NCT00060606) [1].

REFERENCES

1. Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993–1004. doi: 10.1056/NEJMoa1014379. [PubMed: 21306277]
2. Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, et al. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Res A Clin Mol Teratol. 2008;82(7):527–32. doi: 10.1002/bdra.20468. [PubMed: 18481813]
3. Locke MD, Sarwark JF. Orthopedic aspects of myelodysplasia in children. Curr Opin Pediatr. 1996;8(1):65–7. doi: 10.1097/00008480-199602000-00014. [PubMed: 8680519]
4. Beaty JH, Canale ST. Orthopaedic aspects of myelomeningocele. J Bone Joint Surg Am. 1990;72(4):626–30. [PubMed: 2324152]

5. Hullin MG, Robb JE, Loudon IR. Ankle-foot orthosis function in low-level myelomeningocele. J Pediatr Orthop. 1992;12(4):518–21. [PubMed: 1613099]

6. Schiltenwolf M, Carstens C, Rohwedder J, Grundel E. Results of orthotic treatment in children with myelomeningocele. Eur J Pediatr Surg. 1991;1 Suppl 1:50–2. [PubMed: 1807395]

7. Ollesch B, Brazell C, Carry PM, Georgopoulos G. Complications, Results, and Risk Factors of Spinal Fusion in Patients With Myelomeningocele. Spine Deform. 2018;6(4):460–6. doi: 10.1016/j.jspd.2017.12.015. [PubMed: 29886920]

8. Thompson RM, Foley J, Dias L, Swaroop VT. Hip Status and Long-term Functional Outcomes in Spina Bifida. J Pediatr Orthop. 2019;39(3):e168–e72. doi: 10.1097/BPO.0000000000001266. [PubMed: 30300276]

9. Farmer DL, Thom EA, Brock JW 3rd, Burrows PK, Johnson MP, Howell LJ, et al. The Management of Myelomeningocele Study: full cohort 30-month pediatric outcomes. Am J Obstet Gynecol. 2018;218(2):256 e1–e13. doi: 10.1016/j.ajog.2017.12.001. [PubMed: 29246577]

10. Tulipan N, Wellons JC 3rd, Thom EA, Gupta N, Sutton LN, Burrows PK, et al. Prenatal surgery for myelomeningocele and the need for cerebrospinal fluid shunt placement. J Neurosurg Pediatr. 2015;16(6):613–20. doi: 10.3171/2015.7.PEDS15336. [PubMed: 26369371]

11. Cuxart A, Iborra J, Melendez M, Pages E. Physeal injuries in myelomeningocele patients. Paraplegia. 1992;30(11):791–4. doi: 10.1038/sc.1992.152. [PubMed: 1484731]

12. Danielsson AJ, Bartonek A, Levey E, McHale K, Sponseller P, Saraste H. Associations between orthopaedic findings, ambulation and health-related quality of life in children with myelomeningocele. J Child Orthop. 2008;2(1):45–54. doi: 10.1007/s11832-007-0069-6. [PubMed: 19308602]

13. Roiz R, Mueske NM, Van Speybroeck A, Ryan DD, Gilsanz V, Wren TAL. Advanced skeletal maturity in children and adolescents with myelomeningocele. J Pediatr Rehabil Med. 2017;10(3–4):283–93. doi: 10.3233/PRM-170458. [PubMed: 29125519]

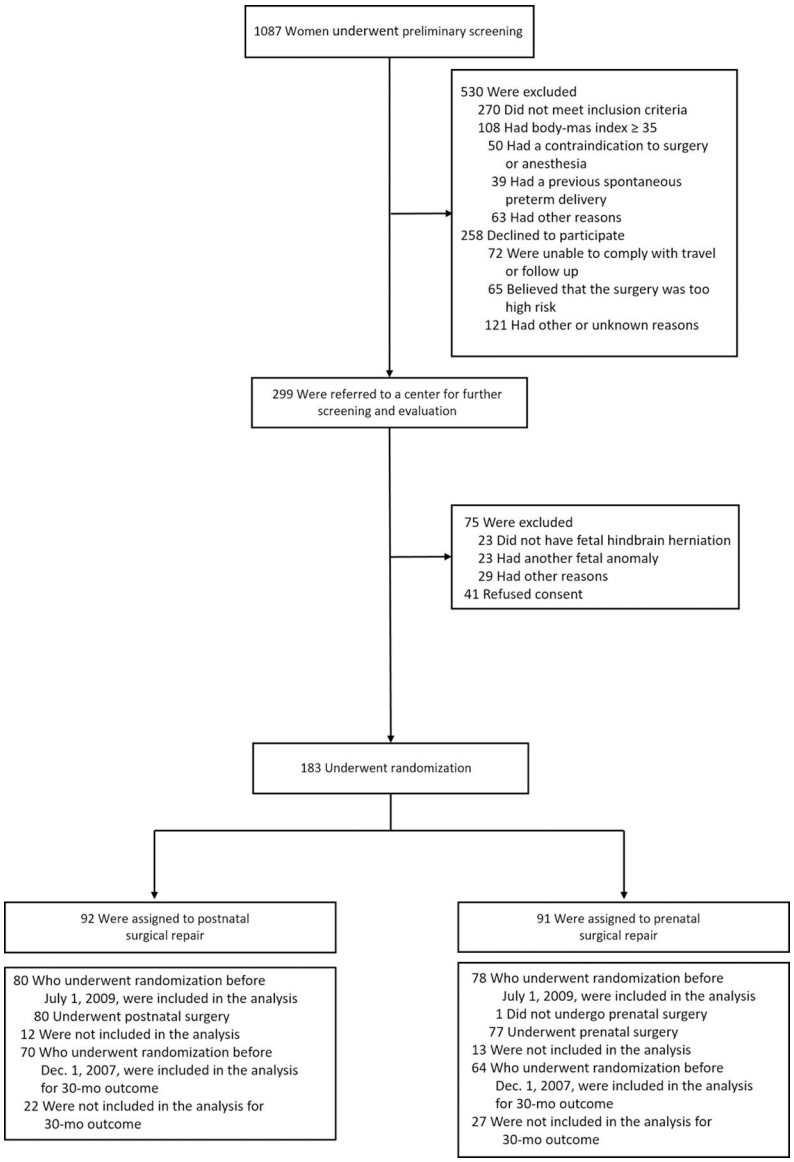

Figure 1:
Enrollment and Outcomes

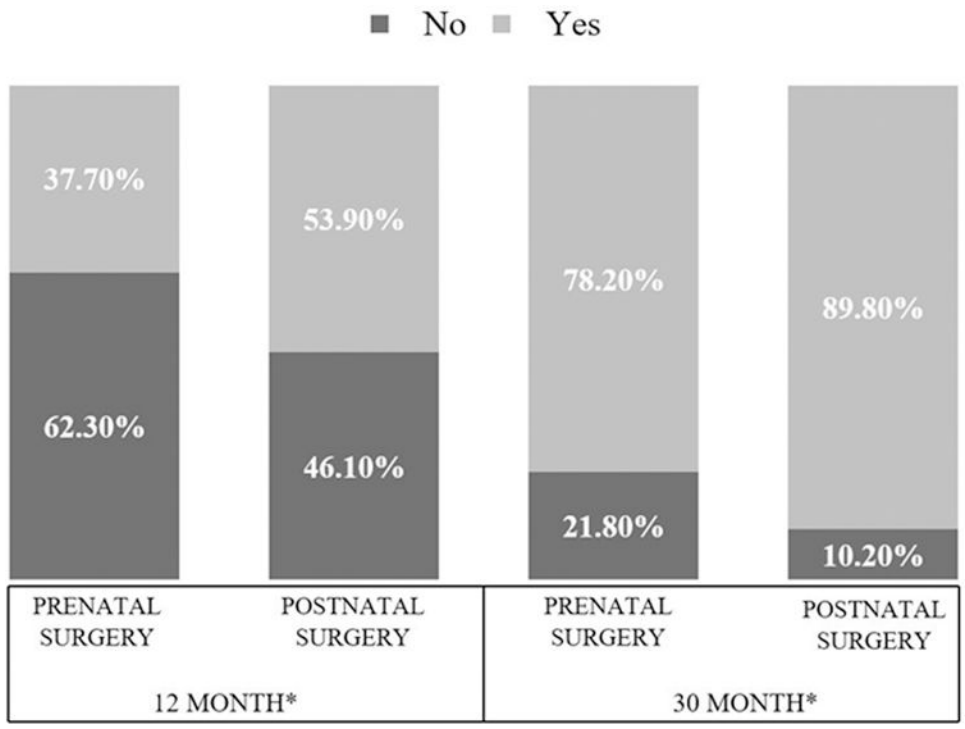

Figure 2:
Rates of treatment for orthopaedic conditions
*Statistically significant at $p < 0.05$

Table 1A.

Baseline Fetal Characteristics

	Prenatal Surgery (n = 91)	**Postnatal Surgery (n = 92)**
Fetal Sex female *	42 (46.2)	57 (62)
Gestational age at randomization, week	23.7 ± 1.4	23.9 ± 1.3
Lesion level, ultrasound *		
Thoracic	4 (4.4)	3 (3.3)
L1-L2	25 (27.5)	13 (14.1)
L3-L4	37 (40.7)	54 (58.7)
L5-S1	25 (27.5)	22 (23.9)
Lesion level ≤ L3	62 (68.1)	76 (82.6)
Clubfoot, ultrasound	24 (26.4)	19 (20.7)
Severe hindbrain herniation	27 (29.7)	23 (25)

* $p \leq 0.05$

Table 1B.

Baseline Maternal Characteristics

	Prenatal Surgery (n = 91)	**Postnatal Surgery (n = 92)**
Maternal age at screening	29.2 ± 5.2	28.7 ± 4.8
Race/Ethnicity		
White	85 (93.4)	86 (93.5)
Black	1 (1.1)	1 (1.1)
Hispanic	3 (3.3)	4 (4.3)
Other	2 (2.2)	1 (1.1)
Married	84 (92.3)	86 (93.5)
Schooling, years	14.9 ± 1.7	14.9 ± 1.7
Body Mass Index at screening	26.3 ± 3.7	26.3 ± 3.9
Current smoker	6 (6.6)	5 (5.4)
Nullipara	37 (40.7)	37 (40.2)
Previous uterine surgery	12 (13.2)	11 (12)

* $p \leq 0.05$

Table 2.

Prevalence of Orthopaedic Conditions after Prenatal and Postnatal Myelomeningocele Repair

Outcome	12 Months		30 Months	
	n	percentage	n	percentage
Scoliosis				
Yes	25	14.4%	34	19.5%
No	149	85.6%	140	80.5%
Kyphosis				
Yes	18	10.3%	31	17.7%
No	156	89.7%	144	82.3%
Leg Length Discrepancy				
Yes	13	7.6%	23	13.1%
No	159	92.4%	152	86.9%
Hip Abnormality [±]				
Yes	46	25.4%		
No	135	74.6%		
Clubfoot at baseline [±]				
Yes	43	23.5%		
No	140	76.5%		
Tibial Torsion [±]				
Yes	10	5.5%		
No	171	94.5%		

[±]This data point was collected only at this time point.

Table 3:

Comparison of prenatal surgery vs. postnatal surgery for orthopaedic conditions after myelomeningocele repair

	12 Months				30 Months			
Outcome	**Prenatal Surgery n (%)**	**Postnatal Surgery n (%)**	**P Value**	**Relative Risk (95% CI)**	**Prenatal Surgery n (%)**	**Postnatal Surgery n (%)**	**P Value**	**Relative Risk (95% CI)**
Scoliosis								
Yes	12 (14.1%)	13 (14.6%)	0.927	.97 (0.46–1.99)	14 (16.3%)	20 (22.7%)	0.283	0.72 (0.38–1.33)
No	73 (85.9%)	76 (85.4%)			72 (83.7%)	68 (77.3%)		
Kyphosis								
Yes	8 (9.4%)	10 (11.2%)	0.693	0.84 (0.35–2.02)	15 (17.2%)	16 (18.2%)	0.871	0.95 (0.50–1.80)
No	77 (90.6%)	79 (88.8%)			72 (82.8%)	72 (81.8%)		
Leg Length Discrepancy								
No	82 (97.6%)	77 (87.5%)	0.012*	0.19 (0.04–0.83)	80 (92.0%	72 (81.8%)	0.047*	0.44 (0.19–1.02)
Yes	2 (2.4%)	11 (12.5%)			7 (8.0%)	16 (18.2%)		
Any Clubfoot at baseline±								
No	67 (73.6%)	73 (79.4%)	0.361	1.28 (0.75–2.16)				
Yes	24 (26.4%)	19 (20.7%)						
Tibial Torsion±								
No	82 (92.1%)	89 (96.7%)	0.175	2.41 (0.64–9.03)				
Yes	7 (7.9%)	3 (3.3%)						
Hip Abnormality±								
No	61 (68.5%)	74 (80.4%)	0.066	1.60 (0.96–2.69)				
Yes	28 (31.5%)	18 (19.6%)						

±This data point was collected only at baseline

*Statistically significant at $p < 0.05$