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Prenatal Repair and Physical Functioning Among Children With Myelomeningocele

A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE The Management of Myelomeningocele Study (MOMS), a randomized clinical trial of prenatal vs standard postnatal repair for myelomeningocele, found that prenatal repair reduced hydrocephalus and hindbrain herniation and improved motor function in children aged 12 to 30 months. The Management of Myelomeningocele Study Follow-up (MOMS2) was conducted in children at ages 5 to 10 years. The primary (neurocognitive) outcome has already been reported.

OBJECTIVE To determine whether MOMS2 participants who had prenatal repair have better physical functioning than those with postnatal repair.

DESIGN, SETTING, AND PARTICIPANTS Participants from MOMS were recruited for participation in the follow-up study, MOMS2, conducted from April 9, 2012, to April 15, 2017. For this secondary analysis of the randomized clinical trial, trained examiners without knowledge of the treatment group evaluated the physical characteristics, self-care skills, neurologic function, and mobility of the children. Physical functioning outcomes were compared between the prenatal and postnatal repair groups. MOMS2 was conducted at the same 3 clinical sites as MOMS. Home visits were conducted for families who were unable to travel to one of the clinical sites. Of the 161 children with myelomeningocele aged 5 to 10 years old enrolled in MOMS2, 154 had a physical examination and were included in the analyses.

EXPOSURES Prenatal repair of myelomeningocele.

MAIN OUTCOMES AND MEASURES Prespecified secondary trial outcomes of self-care skills, functional mobility, walking skills, and motor level.

RESULTS This analysis included 78 children with postnatal repair (mean [SD] age, 7.4 [2.1] years; 50 girls [64.1%]; 69 White children [88.5%]) and 76 with prenatal repair (mean [SD] age, 7.5 [1.2] years; 43 boys [56.6%]; 70 White children [92.1%]). Children in the prenatal repair group were more competent with self-care skills (mean [SD] percentage of maximum FRESNO Scale score, 90.8% [9.6%] vs 85.5% [17.6%]) and were commonly community ambulators per the Modified Hoffer Classification (51.3% prenatal vs 23.1% postnatal; adjusted relative risk [aRR] for sex, 1.70; 95% CI, 1.23-2.34). Children with prenatal repair also performed the 10-m walk test 1 second faster (difference in medians, 1.0; 95% CI, 0.3-1.7), had better gait quality (adjusted mean difference for home distances of 5 m, 1.71; 95% CI, 1.14-2.54), and could perform higher-level mobility skills (adjusted mean difference for motor total, 5.70; 95% CI, 1.97-11.18). Children in the prenatal repair group were less likely to have a motor function level worse than their anatomic lesion level (aRR, 0.44; 95% CI, 0.25-0.77).

CONCLUSIONS AND RELEVANCE This secondary analysis of a randomized clinical trial found that the physical functioning benefits of prenatal repair for myelomeningocele reported at age 30 months persisted into school age. These findings indicate the benefit of prenatal repair of myelomeningocele for school-aged children.

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Supplemental content
Editorial

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Myelomeningocele, a complex congenital anomaly caused by incomplete neural tube closure during embryonic development, affects approximately 1 in 1500 to 3300 births in the United States annually.[1,2] Individuals with myelomeningocele have lower extremity sensory and motor dysfunction as well as long-term neurodevelopmental sequelae that affect motor skills, self-care, bladder and bowel control, and cognition.[3-10] Despite recent advances in the treatment of myelomeningocele, individuals tend to have some level of persistent and lifelong disability.[5,7,11]

The Management of Myelomeningocele Study (MOMS), a randomized controlled clinical trial to compare the safety and efficacy of prenatal repair of myelomeningocele with standard postnatal repair, demonstrated improved outcomes for children who had prenatal repair.[12] Fewer infants in the prenatal repair group needed ventriculoperitoneal shunting for hydrocephalus, and at 30 months of age, they had a better score for a composite of mental development and difference between motor and anatomic lesion level.[12] At 30 months, more children in the prenatal repair group were able to walk independently and had better self-care skills.[13] The follow-up study, MOMS2, was conducted between 2012 and 2017 to assess adaptive behavior, neurocognition, urologic function, physical functioning, quality of life, and effect on the family. The primary outcome, the composite score from the Vineland Adaptive Behavior Scales, did not differ between the prenatal and postnatal repair groups.[14] However, the prenatal repair group was noted to have better scores on some of the neuropsychological tests and on a composite evaluation of self-care and mobility derived from the Functional Rehabilitation Evaluation Sensori-Neurological Outcomes (FRESNO) Scale instrument, and more commonly achieved independent walking.[14] Additionally, children in the prenatal repair group were more likely to void volitionally and less likely to use intermittent straight catheterization.[15]

The purpose of the current analysis was to evaluate the prespecified secondary outcome of physical functioning by comparing the physical functioning skills of children in the prenatal and postnatal repair groups at school age. Consistent with the better functioning skills at 30 months shown in the original trial, we hypothesized that children in the prenatal repair group would continue to have better self-care and mobility skills at school age and would have better motor levels compared with anatomic levels than children in the postnatal repair group.

Key Points

Question Do children who have undergone prenatal repair of myelomeningocele have better functional mobility and motor levels than school-aged children who have had standard postnatal repair?

Findings In this secondary analysis of 154 children from the Management of Myelomeningocele Study randomized clinical trial, 51.3% of children who underwent prenatal repair could independently walk community distances compared with 23.1% of children who underwent standard postnatal repair. Children in the prenatal repair group were less likely to have a motor function level worse than their anatomic lesion level (adjusted relative risk, 0.44).

Meaning These findings suggest that functional mobility and motor levels are improved for children who underwent prenatal myelomeningocele repair vs standard postnatal repair.

Methods

This study is a prespecified secondary analysis of MOMS2, which was conducted from April 9, 2012, and April 15, 2017, with 161 children from the MOMS trial at the same 3 centers (Children's Hospital of Philadelphia, Vanderbilt University Medical Center, and the University of California, San Francisco) along with the data coordinating center at the George Washington University Biostatistics Center. Institutional review board approval was obtained at each site. Caregivers gave written informed consent, and children gave assent per institutional regulations.

Full details of the study procedures are available elsewhere.[14] Briefly, participation consisted of a comprehensive study visit when the child was aged between 5 and 10 years, which took place at 1 of the clinical centers or, if the caregiver declined to travel, at the child's home. Children underwent a physical examination and functioning assessment by a study-designated trained physical therapist or physiatrist (J.J.-C., L.F., A.J.H., or M.R.). In addition, the caregiver completed a demographic information form and validated questionnaires. The examiners were blinded to treatment group, and caregivers were asked to refrain from mentioning their child's surgical repair group.

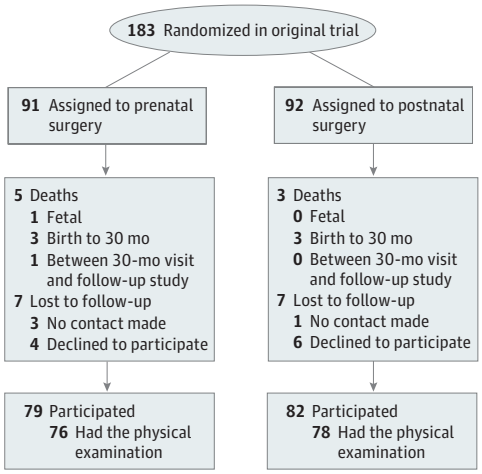
Physical Functioning Outcomes

Height, arm span, head circumference, and weight were measured. Body mass index was calculated per the usual formula (weight in kilograms divided by height in meters squared) as well as substituting the child's arm span for height to enable comparison with the body mass index of unaffected children. The examiners also reported on the presence of scoliosis, kyphosis, lordosis, leg length discrepancies, varus or valgus knees, foot deformities, contractures at the hip, knee, and ankle, and spasticity.

Functional skills were measured using 34 items preselected from the FRESNO Scale, a validated measure of functioning devised for children with disabilities.[16] The questions were classified into 3 categories: self-care, motor, and recreational (question provided in eTable 1 in the Supplement).

To assess walking, the children were classified using the Functional Mobility Scale, which measures the type of assistive device (if any) the child requires to ambulate household, school, and community distances.[17] Children were also classified into 3 groups using an accepted modified version of the Hoffer classification system (community ambulators, household ambulators, and nonambulators).[18,19] For children who were able to walk, gait speed was measured using the 10-m walk test.[20,21] Children were instructed to use all of their regular equipment (orthotics and assistive devices) to walk at a comfortable pace and were measured over 3 attempts, with the

Figure. Flow Diagram for Enrollment and Follow-up



mean measurement being used for analysis. The 10-m walk test trials were video recorded from 3 angles (behind the child, in front of the child, and along the side of the child) for central review of gait quality and gait style (alternating limbs, swing-through or swing-to). For those who had an alternating gait style, initial contact (heel, foot, or forefoot and toes), pre-swing phase (forefoot and toes, foot, or heel), stride lengths and symmetry, and gait stability were assessed. Trunk and limb characteristics during gait were also compared: excessive lordosis, forward-flexed trunk, pelvic obliquity, Trendelenburg (trunk lean), excessive pelvic rotation, hip circumduction, hip hiking, crouch gait, knee hyperextension, limb dragging, and limb external and internal rotation.

All children were assessed in their ability to sit without support, to get from a supine to sitting position, to get from sitting to standing, and to stand independently for 10 seconds. For ambulators, more advanced motor skills were assessed: jumping, single-legged stance, hopping at least 3 times, galloping, skipping, ascending and descending stairs, walking backward, tandem walking, heel walking, toe walking, and getting up and down from a squat. For wheelchair users, wheelchair transfers from a surface level with their wheelchair and from the ground were assessed.

The Broughton scale, which relies on manual muscle testing of various lower extremity muscles to assign motor levels, was used.[22] The association between anatomic level (as measured on the x-ray of the spine performed at the 1-year visit in the MOMS trial)[12] and motor level was assessed.

Statistical Analysis

All analyses were adjusted for child sex, the single baseline variable known to be significantly different between groups in the original trial. Each item on the FRESNO Scale is scored as 0 (dependent), 1 (requires assistance), or 2 (can perform the skill independently); owing to the infrequency of the scores 0 and 1, we combined scores 0 and 1 to create a dichotomous variable. For these and other dichotomous outcome variables, Mantel-Haenszel relative risks (RRs) and 95% CIs are reported.

Table 1. Baseline Characteristics of the Sample

Characteristic	No. (%)[a]	
	Prenatal (n = 76)	Postnatal (n = 78)
Age of child at MOMS2 visit (SD), y	7.5 (1.2)	7.4 (1.2)
Female sex	33 (43.4)	50 (64.1)
Child's race/ethnicity		
White non-Hispanic	70 (92.1)	69 (88.5)
Black non-Hispanic	1 (1.3)	1 (1.3)
Hispanic	3 (4.0)	5 (6.4)
Other	2 (2.6)	3 (3.9)
Anatomic lesion level		
Thoracic	2 (2.6)	1 (1.3)
L1	4 (5.3)	5 (6.4)
L2	7 (9.2)	9 (11.5)
L3	20 (26.3)	11 (14.1)
L4	16 (21.1)	26 (33.3)
L5	18 (23.7)	26 (33.3)
S1	8 (10.5)	0
S2	1 (1.3)	1 (1.3)
Gestational age at birth (SD), wk	34.4 (2.6)	37.4 (1.0)

Abbreviation: MOMS2, Management of Myelomeningocele Study Follow-up.

[a] Values expressed as No. (%) unless otherwise specified.

The FRESNO Scale domain scores were expressed as a percentage of the maximum score for the 3 categories tested: self-care, motor, and recreation. The arcsine transformation was used to approximate the normal distribution. For this and other continuous variables, a general linear regression model was used to provide point estimates of the treatment effect with 95% CIs. The Van Elteren test was used to compare groups on the 10-m walk test, where those who could not walk were given the highest rank.

The widths of CIs have not been adjusted for multiplicity, and thus, the inferences drawn may not be robust. All P values were 2 sided, and $P < .05$ was considered significant. The statistical analysis was performed using SAS, version 9.4 (SAS Institute Inc), and the plan is provided in the protocol.

Results

Baseline and Anatomic Characteristics of the Sample

A total of 161 of the 183 families who were enrolled in the MOMS trial participated in MOMS2, and 154 children received the physical functioning assessment (**Figure**). Of those 154 children, 78 underwent postnatal repair (mean [SD] age, 7.4 [2.1] years; 50 girls [64.1%]; 69 White children [88.5%]), and 76 underwent prenatal repair (mean [SD] age, 7.5 [1.2] years; 43 boys [56.6%]; 70 White children [92.1%]). As observed previously,[12,14] children in the prenatal group were less commonly girls and were born 3 weeks earlier than those in the postnatal group (mean [SD] gestational age at birth, 34.4 [2.6] weeks vs 37.4 [1.0] weeks) (**Table 1**). The mean age of the children at the physical evaluation did not differ by repair group. Physical findings are shown in **Table 2**. There were no differences in anthropometric measurements between the 2 groups.

Table 2. Physical Findings of MOMS2 Children by Repair Status

Variable[a]	No. (%)[b]		Adjusted mean difference (95% CI) or adjusted relative risk (95% CI)[c]
	Prenatal repair (n = 76)	Postnatal repair (n = 78)	
Anthropometric measurements			
Height/length, mean (SD), cm	120.6 (10.9)	116.8 (9.7)	3.9 (0.5 to 7.3)
Arm span, mean (SD), cm	123.5 (10.9)	122.1 (10.8)	1.6 (−2.0 to 5.2)
Weight, mean (SD), kg	26.3 (7.7)	25.9 (7.1)	0.5 (−1.9 to 2.9)
Head circumference, mean (SD), cm	53.2 (2.3)	52.1 (2.7)	1.1 (0.2 to 1.9)
BMI using height/length,[d] mean (SD)	17.8 (2.8)	18.6 (3.1)	−0.9 (−1.8 to 0.1)
BMI using arm span,[e] mean (SD)	16.9 (2.8)	17.1 (3.0)	−0.1 (−1.1 to 0.8)
Deformities			
Scoliosis	14 (18.4)	25 (32.1)	0.60 (0.34 to 1.05)
Kyphosis	4 (5.3)	5 (6.4)	0.74 (0.19 to 2.86)
Excessive lordosis	10 (13.2)	13 (16.7)	0.80 (0.37 to 1.72)
Leg length discrepancy	14 (18.4)	24 (30.8)	0.63 (0.34 to 1.16)
Valgus or varus knee deformity	12 (15.8)	14 (17.9)	0.87 (0.42 to 1.80)
Foot deformity	47 (62.7)	49 (63.6)	1.02 (0.80 to 1.30)
Spasticity	6 (7.9)	8 (10.3)	0.75 (0.28 to 2.00)
Contractures[f]			
Hip	8 (10.5)	17 (22.1)	0.44 (0.19 to 1.01)
Knee	11 (14.5)	28 (36.4)	0.39 (0.21 to 0.72)
Ankle	60 (80.0)	71 (92.2)	0.85 (0.75 to 0.97)

Abbreviations: BMI, body mass index; MOMS2, Management of Myelomeningocele Study Follow-up.

[a] One child in the prenatal repair group and 2 children in the postnatal repair group were missing weight. In addition, 1 child in the postnatal repair group was missing head circumference, and another was missing arm span.

[b] Values expressed as No. (%) unless otherwise specified.

[c] Adjusted for child sex. Adjusted mean differences are presented for anthropometric measurements; adjusted relative risk, for deformities.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Calculated as weight in kilograms divided by arm span in meters squared.

[f] Data for contractures missing for 1 child in the postnatal repair group.

Children in the prenatal repair group were more competent with self-care skills and were commonly community ambulators per the Modified Hoffer Classification (51.3% prenatal vs 23.1% postnatal; adjusted relative risk [aRR] for child sex, 1.70; 95% CI, 1.23-2.34). Most children in both repair groups had foot deformities, but there were fewer contractures in the prenatal surgery group: 11 of 76 (14.5%) had knee contractures and 60 of 76 (80.0%) had ankle contractures compared with 28 of 77 (36.4%) and 71 of 77 (92.2%), respectively, in the postnatal group (knee contracture aRR, 0.39; 95% CI, 0.21-0.72; ankle contracture aRR, 0.85; 95% CI, 0.75-0.97). There were no differences in the percentages of children with spasticity, knee deformities, leg length discrepancies, scoliosis, or kyphosis.

Self-care Skills

Children in the prenatal repair group performed a higher overall percentage of age-appropriate self-care skills (mean [SD] percentage of maximum FRESNO Scale score, 90.8% [9.6%]) than children in the postnatal repair group (mean [SD] percentage of maximum FRESNO Scale score, 85.5% [17.6%]; adjusted mean difference, 1.04; 95% CI, 0.08-3.00) (**Table 3**). This difference is driven by independence with chewing and swallowing (aRR, 1.10; 95% CI, 1.02-1.19), using a fork (aRR, 1.08; 95% CI, 1.10-1.16), brushing teeth (aRR, 1.21; 95% CI, 1.05-1.38), washing and drying hands (aRR, 1.13; 95% CI, 1.02-1.24), doffing pants (aRR, 1.13; 95% CI, 1.01-1.26), doffing socks (aRR, 1.07; 95% CI, 1.01-1.14), and zipping and unzipping (aRR, 1.24; 95% CI, 1.03-1.49) (eTable 1 in the Supplement). Similarly, children in the prenatal repair group performed better in the motor category than children in the postnatal repair group (93.6% vs 80.5%; adjusted mean difference, 5.7; 95% CI, 2.0-11.2). There was not a significant difference in the recreational skills category between the 2 groups.

Functional Mobility

Mobility was also assessed with both the Functional Mobility Scale and the Hoffer Functional Ambulation Scale (Table 3). At each distance (home, school and community), children in the prenatal repair group were more likely to be independent with ambulation compared with children in the postnatal repair group (adjusted mean difference for home distances of 5 m, 1.71; 95% CI, 1.14-2.54; for school distances of 50 m, 1.93; 95% CI, 1.21-3.06; for community distances of 500 m, 2.21; 95% CI, 1.33-3.65). Children in the prenatal repair group were 70% more likely to walk independently in the community (aRR, 1.70; 95% CI, 1.23-2.34) than children in the postnatal repair group. During the observed gait evaluation (eTable 2 in the Supplement), more than two-thirds (53 of 77 [68.8%]) of children in the prenatal repair group did not require an assistive device to ambulate at least 20 feet compared with less than half (35 of 78 [44.9%]) of the children in the postnatal repair group (aRR 1.54; 95% CI 1.12-2.12). Among ambulators, children in the prenatal repair group were more than twice as likely to walk without bracing compared with children in the postnatal repair group (22 of 68 [32.4%] vs 9 of 59 [15.3%]; aRR, 2.4; 95% CI, 1.05-5.49).

Table 3. Functional Skills and Ambulation by Repair Status

Variable	No. (%)[a]		Adjusted mean difference (95% CI) or adjusted relative risk (95% CI)[b]
	Prenatal repair (n = 76)	Postnatal repair (n = 78)	
FRESNO Scale, mean (SD), % of maximum score			
Self-care total	90.8 (9.6)	85.5 (17.6)	1.04 (0.08-3.00)
Motor (transfer & mobility) total	93.6 (14.2)	80.5 (25.6)	5.70 (1.97-11.18)
Recreation total	94.7 (11.9)	90.0 (20.3)	0.83 (0-3.38)
Functional Mobility Scale			
Home distances, 5 m			
Wheelchair	7 (9.2)	22 (28.2)	1.71 (1.14-2.54)
Walker or gait trainer	6 (7.9)	10 (12.8)	
Crutches bilaterally	5 (6.6)	9 (11.5)	
Single crutch or cane	1 (1.3)	0	
No walking aids (may use handrails)	13 (17.1)	11 (14.1)	
Totally independent	44 (57.9)	26 (33.3)	
School distances, 50 m			
Wheelchair	10 (13.2)	29 (37.2)	1.93 (1.21-3.06)
Walker or gait trainer	4 (5.3)	13 (16.7)	
Crutches bilaterally	11 (14.5)	8 (10.3)	
Single crutch or cane	2 (2.6)	1 (1.3)	
No walking aids (may use handrails)	9 (11.8)	6 (7.7)	
Totally independent	40 (52.6)	21 (26.9)	
Community distances, 500 m			
Wheelchair	17 (22.4)	40 (51.3)	2.21 (1.33-3.65)
Walker or gait trainer	5 (6.6)	6 (7.7)	
Crutches bilaterally	5 (6.6)	5 (6.4)	
Single crutch or cane	2 (2.6)	2 (2.6)	
No walking aids (may use handrails)	8 (10.5)	7 (9.0)	
Totally independent	39 (51.3)	18 (23.1)	
Modified Hoffer Classification[c]			
Community ambulator	54 (71.1)	32 (41.0)	1.70 (1.23-2.34)
Household ambulator	15 (19.7)	24 (30.8)	
Nonambulator	7 (9.2)	22 (28.2)	
10-m Walk test			
Median time (95% CI), s	4.7 (4.6-5.0)	5.7 (5.0-6.7)	NA
Difference (95% CI),[d] s	1.0 (0.3-1.7)		

Abbreviations: FRESNO, Functional Rehabilitation Evaluation Sensori-Neurological Outcomes; NA, not applicable.

[a] Values expressed as No. (%) unless otherwise specified.

[b] Adjusted for child sex. Adjusted mean differences are presented for FRESNO Scale outcomes; adjusted relative risks for totally independent vs other are presented for Functional Mobility Scale outcomes; and adjusted relative risks for community ambulator vs others are presented for Modified Hoffer Classification outcomes.

[c] Community ambulator walks independently or using devices at community distances; household ambulator walks independently or using devices short but not community distances; nonambulator uses a wheelchair for mobility.

[d] Hodges-Lehmann estimate.

Gait Quality

The quality of the children's gait among ambulators also differed by repair status (eTable 2 in the Supplement). Nearly all of the children (55 of 60 [91.7%]) in the prenatal repair group had symmetric strides compared with 39 of 53 (73.6%) in the postnatal repair group (aRR, 1.26; 95% CI, 1.03-1.54). Further, of those able to alternate their feet, only 3 of 60 (5%) had short strides compared with 18 of 53 (34%) in the postnatal repair group (aRR, 0.13; 95% CI, 0.04-0.43). Although a large majority of the children able to walk in the prenatal repair group had stable gaits (52 of 60 [86.7%]), this was true for only 26 of 53 (49.1%) of the children in the postnatal repair group (aRR, 1.87; 95% CI, 1.35-2.58). Children in the prenatal repair group had lower risk of excessive lordosis (aRR, 0.55; 95% CI, 0.33-0.90) and Trendelenburg gait (aRR, 0.40; 95% CI, 0.25-0.64). Children in the prenatal repair group completed the 10-m walk test 1 second faster than those in the postnatal repair group (median time, 4.7 [95% CI, 4.6-5.0] seconds vs 5.7 [95% CI, 0.3-1.7] seconds; $P = .004$).

Motor Skills and Motor Levels

Children in the prenatal repair group could perform higher-level mobility skills (adjusted mean difference for motor total, 5.70; 95% CI, 1.97-11.18). They were more likely to be independent with the following skills: sit to stand (aRR, 1.28; 95% CI, 1.08-1.52), standing for more than 10 seconds (aRR, 1.40; 95% CI, 1.15-1.71), jumping (aRR, 1.84; 95% CI, 1.32-2.57), hopping at least 3 times (aRR, 7.57; 95% CI, 1.80-31.8), galloping (aRR, 2.97; 95% CI, 1.31-6.74), skipping (aRR, 6.24; 95% CI, 1.95-19.90), ascending and descending stairs (ascending aRR, 1.29;

Table 4. Motor Levels as Assessed by the Broughton Scale and Motor to Anatomic Level Comparisons by Repair Status

Broughton scale	No. (%)[a] Prenatal (n = 76)	Postnatal (n = 77)
Thoracic	3 (4.0)	11 (14.3)
L1	9 (11.8)	13 (16.9)
L2	0 (0)	1 (1.3)
L3	3 (4.0)	5 (6.5)
L4	18 (23.7)	28 (36.4)
L5	1 (1.3)	0 (0)
S1	30 (39.5)	16 (20.8)
S2	12 (15.8)	3 (3.9)
Comparison of motor level with anatomic level		
Motor level ≥2 levels worse than anatomic	9 (11.8)	18 (23.4)
Motor level 1 level worse than anatomic	6 (7.9)	15 (19.5)
Motor level = anatomic level	12 (15.8)	16 (20.8)
Motor level 1 level better than anatomic	22 (29.0)	17 (22.1)
Motor level ≥2 levels better than anatomic	27 (35.5)	11 (14.3)
Adjusted relative risk (95% CI) for motor level worse than anatomic[b]	0.44 (0.25-0.77)	

[a] Values expressed as No. (%) unless otherwise specified.

[b] Adjusted for child sex.

95% CI, 1.07-1.56; descending aRR, 1.28; 95% CI, 1.05-1.57), walking backward (aRR, 1.75; 95% CI, 1.29-2.39), tandem walking (aRR, 2.87; 95% CI, 1.02-8.09), walking on toes (aRR, 2.48; 95% CI, 1.19-5.17), and getting into and up from squat (aRR 1.87; 95% CI, 1.29-2.70) (eTable 3 in the Supplement). Children in the prenatal repair group were less than half as likely (aRR, 0.44; 95% CI, 0.25-0.77) to have motor levels that were worse than their anatomic levels (**Table 4**), compared with children in the postnatal repair group.

Discussion

These results show that children with prenatally repaired myelomeningocele demonstrated superior performance compared with children who had standard postnatal repair on measures of self-care, motor function, and mobility. Not only were the children in the prenatal repair group more likely to walk, but they less frequently needed bracing and assistive devices to do so. The speed and quality of their gaits were better, and they were more adept at advanced motor skills, such as walking up and down stairs, compared with children in the postnatal repair group—all indicating the increased ease of performing daily motor activities in their lives. The data presented here demonstrate that the benefits of prenatal repair on mobility persist beyond 30 months. This is especially important because of previously raised concerns that the advantages from prenatal surgery may decrease over time, as most children with myelomeningocele have gross motor developmental delays secondary to abnormalities of the spinal cord, brainstem, and cerebellum[23] and are, therefore, delayed ambulators.[18,24] Additionally, motor function can change during childhood for children with myelomeningocele, especially for those with symptomatic tethered cord.[23-27] Spasticity, a common finding of tethered cord, was not differentially present between the prenatal and postnatal repair groups in this study, although there was a significant difference between the groups for tethered cord release.[14] The findings presented here indicate that despite the higher rates of tethered cord releases, a longstanding concern among clinicians,[28] children in the prenatal group maintained better motor function.

Consistent with the findings in MOMS,[12,13] children who had prenatal repair more frequently had motor levels that were 1 or more levels better than their anatomic levels. This finding was also noted in a single-center cohort post-MOMS.[29,30] Functional motor level is of primary importance when clinically predicting future ambulation, as almost all patients with quadriceps function are able to walk (though often with bracing),[18] whereas children with sacral level lesions are nearly uniformly community ambulators.[23,31] In this study, there appeared to be a long-term benefit from neural protection in utero in terms of both motor level and functional skills that require lower extremity strength at school age. These findings support the pathophysiologic theory of the 2-hit phenomenon in which fetuses with myelomeningocele have primary neurulation failure followed by neural tissue damage from neurotoxic intrauterine contents.[29] Besides the strong association between motor level and ambulation, a number of other factors are associated with successful ambulation.[3] The presence of hydrocephalus requiring a ventriculoperitoneal shunt has been found to be inversely associated with ambulation.[3] In MOMS, children in the prenatal repair group less commonly needed shunts.[12,32] Additionally, hindbrain abnormalities, which were less common among the prenatal repair group,[14] are also known to impair the ability to ambulate owing to damage to the corticospinal tract.[3,33] The presence of contractures, which was less common in the prenatal repair group, is inversely associated with ambulation.[34-36] Lastly, prolonged immobilization, often associated with surgeries, which were less common in the prenatal repair group,[14] is associated with a decline in ambulation ability.[35,37]

Children in the prenatal repair group performed better in self-care activities. Children with myelomeningocele tend to perform poorly on fine motor tasks and self-care activities compared with their age-matched peers, a finding strongly correlated with the presence of hydrocephalus,[38] which was less problematic in children after prenatal repair.[12] In MOMS2, the children in the prenatal repair group performed better on the Purdue Pegboard Test, a measure of dexterity,[14] likely owing to the reduced hindbrain herniation seen with prenatal repair, which may help explain why the children who had prenatal repair performed better on self-care skills that require dexterity. Schoenmakers et al[39] found that intact quadriceps strength and the absence of contractures were positively associated with independence in self-care activities. In MOMS2, children who had prenatal repair had better motor strength and fewer contractures. Additionally, children in the prenatal repair group had less hindbrain

herniation, which may explain why they more commonly could chew and swallow all textures of foods than the children in the postnatal repair group.[14]

Limitations

This project has limitations. First, we were unable to recruit all of the families involved in the original MOMS trial, and not all of those recruited completed the physical functioning assessment and questionnaires. Second, parents were not blinded to their child's surgical group, which could have biased their responses on questionnaires. Finally, the generalizability of the study is limited because the study sample contained predominately White non-Hispanic children with an underrepresentation of Hispanic children based on the known prevalence of myelomeningocele in the United States.[1]

Conclusions

In this secondary analysis of the MOMS trial, children with prenatal repair of myelomeningocele performed better than children with postnatal repair regarding self-care and mobility tasks. Children who underwent prenatal repair had improved motor levels compared with their anatomic levels, walked faster and better with less assistance, and could perform more advanced motor skills. These data indicate the benefit of prenatal repair for myelomeningocele for school-aged children. Long-term follow-up of motor skills, ambulatory status, and executive functioning is needed to determine the sustained effects of prenatal repair for myelomeningocele on mobility and functional independence.[40]

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REFERENCES

1. Agopian AJ, Canfield MA, Olney RS, et al; National Birth Defects Prevention Study. Spina bifida subtypes and sub-phenotypes by maternal race/ethnicity in the National Birth Defects Prevention Study. *Am J Med Genet A*. 2012;158A(1):109-115. doi:10.1002/ajmg.a.34383

2. Parker SE, Mai CT, Canfield MA, et al; National Birth Defects Prevention Network. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol*. 2010;88(12):1008-1016. doi:10.1002/bdra.20735

3. Dicianno BE, Karmarkar A, Houtrow A, et al. Factors associated with mobility outcomes in a national spina bifida patient registry. *Am J Phys Med Rehabil*. 2015;94(12):1015-1025. doi:10.1097/PHM.0000000000000404

4. Tita AC, Frampton JR, Roehmer C, Izzo SE, Houtrow AJ, Dicianno BE. Correlation between neurologic impairment grade and ambulation status in the adult spina bifida population. *Am J Phys Med Rehabil*. 2019;98(12):1045-1050. doi:10.1097/PHM.0000000000001188

5. Dicianno BE, Bellin MH, Zabel AT. Spina bifida and mobility in the transition years. *Am J Phys Med Rehabil*. 2009;88(12):1002-1006. doi:10.1097/PHM.0b013e3181c1ede3

6. Dennis M, Barnes MA. The cognitive phenotype of spina bifida meningomyelocele. *Dev Disabil Res Rev*. 2010;16(1):31-39. doi:10.1002/ddrr.89

7. Houtrow A, Dicianno BE. Advances in spina bifida care: from the womb to adulthood. *Curr Phys Med Rehabil Rep* 2014;2:71-78. doi:10.1007/s40141-014-0046-1

8. Norrlin S, Strinnholm M, Carlsson M, Dahl M. Factors of significance for mobility in children with myelomeningocele. *Acta Paediatr*. 2003;92(2):204-210. doi:10.1111/j.1651-2227.2003.tb00527.x

9. Fletcher JM, Ostermaier KK, Cirino PT, Dennis M. Neurobehavioral outcomes in spina bifida: processes versus outcomes. *J Pediatr Rehabil Med*. 2008;1(4):311-324.

10. Fletcher JM, Copeland K, Frederick JA, et al. Spinal lesion level in spina bifida: a source of neural and cognitive heterogeneity. *J Neurosurg*. 2005;102(3 suppl):268-279. doi:10.3171/ped.2005.102.3.0268

11. Danzer E, Johnson MP, Adzick NS. Fetal surgery for myelomeningocele: progress and perspectives. *Dev Med Child Neurol*. 2012;54(1):8-14. doi:10.1111/j.1469-8749.2011.04049.x

12. Adzick NS, Thom EA, Spong CY, et al; MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. *N Engl J Med*. 2011;364(11):993-1004. doi:10.1056/NEJMoa1014379

13. Farmer DL, Thom EA, Brock JW III, et al; Management of Myelomeningocele Study Investigators. The Management of Myelomeningocele Study: full cohort 30-month pediatric outcomes. *Am J Obstet Gynecol*. 2018;218(2):256.e1-256.e13. doi:10.1016/j.ajog.2017.12.001

14. Houtrow AJ, Thom EA, Fletcher JM, et al. Prenatal repair of myelomeningocele and

school-age functional outcomes. *Pediatrics*. 2020;145(2):e20191544. doi:10.1542/peds.2019-1544

15. Brock JW III, Thomas JC, Baskin LS, et al; Eunice Kennedy Shriver NICHD MOMS Trial Group. Effect of prenatal repair of myelomeningocele on urological outcomes at school age. *J Urol*. 2019;202(4):812-818. doi:10.1097/JU.0000000000000334

16. Roberts SD, Wells RD, Brown IS, et al. The FRESNO: a pediatric functional outcome measurement system. *J Rehabil Outcomes Meas*. 1999;3:11-99.

17. Graham HK, Harvey A, Rodda J, Nattrass GR, Pirpiris M. The Functional Mobility Scale (FMS). *J Pediatr Orthop*. 2004;24(5):514-520. doi:10.1097/01241398-200409000-00011

18. Swank M, Dias L. Myelomeningocele: a review of the orthopaedic aspects of 206 patients treated from birth with no selection criteria. *Dev Med Child Neurol*. 1992;34(12):1047-1052. doi:10.1111/j.1469-8749.1992.tb11416.x

19. Hoffer MM, Feiwell E, Perry R, Perry J, Bonnett C. Functional ambulation in patients with myelomeningocele. *J Bone Joint Surg Am*. 1973;55(1):137-148. doi:10.2106/00004623-197355010-00014

20. Graser JV, Letsch C, van Hedel HJA. Reliability of timed walking tests and temporo-spatial gait parameters in youths with neurological gait disorders. *BMC Neurol*. 2016;16:15. doi:10.1186/s12883-016-0538-y

21. Poncumhak P, Saengsuwan J, Kamruecha W, Amatachaya S. Reliability and validity of three functional tests in ambulatory patients with spinal cord injury. *Spinal Cord*. 2013;51(3):214-217. doi:10.1038/sc.2012.126

22. Broughton NS, Menelaus MB, Cole WG, Shurtleff DB. The natural history of hip deformity in myelomeningocele. *J Bone Joint Surg Br*. 1993;75(5):760-763. doi:10.1302/0301-620X.75B5.8376434

23. Schoenmakers MA, Gulmans VA, Gooskens RH, Helders PJ. Spina bifida at the sacral level: more than minor gait disturbances. *Clin Rehabil*. 2004;18(2):178-185. doi:10.1191/0269215504cr718oa

24. Worley G. A clinician's concerns about motor function outcomes of fetal surgery for myelomeningocele. *Am J Obstet Gynecol*. 2019;220(1):124. doi:10.1016/j.ajog.2018.09.020

25. McDonald CM, Jaffe KM, Shurtleff DB. Assessment of muscle strength in children with meningomyelocele: accuracy and stability of measurements over time. *Arch Phys Med Rehabil*. 1986;67(12):855-861.

26. McDonald CM, Jaffe KM, Mosca VS, Shurtleff DB. Ambulatory outcome of children with myelomeningocele: effect of lower-extremity muscle strength. *Dev Med Child Neurol*. 1991;33(6):482-490. doi:10.1111/j.1469-8749.1991.tb14913.x

27. Danzer E, Thomas NH, Thomas A, et al. Long-term neurofunctional outcome, executive functioning, and behavioral adaptive skills following fetal myelomeningocele surgery. *Am J Obstet Gynecol*. 2016;214(2):269.e1-269.e8. doi:10.1016/j.ajog.2015.09.094

28. Mazzola CA, Tyagi R, Assassi N, et al. Congress of Neurological Surgeons systematic review and evidence-based guideline on the incidence of tethered cord syndrome in infants with myelomeningocele with prenatal versus postnatal repair. *Neurosurgery*. 2019;85(3):E417-E419. doi:10.1093/neuros/nyz266

29. Dewan MC, Wellons JC. Fetal surgery for spina bifida. *J Neurosurg Pediatr*. 2019;24(2):105-114. doi:10.3171/2019.4.PEDS18383

30. Moldenhauer JS, Soni S, Rintoul NE, et al. Fetal myelomeningocele repair: the post-MOMS experience at the Children's Hospital of Philadelphia. *Fetal Diagn Ther*. 2015;37(3):235-240. doi:10.1159/000365353

31. Asher M, Olson J. Factors affecting the ambulatory status of patients with spina bifida cystica. *J Bone Joint Surg Am*. 1983;65(3):350-356. doi:10.2106/00004623-198365030-00009

32. Tulipan N, Wellons JC III, Thom EA, et al; MOMS Investigators. Prenatal surgery for myelomeningocele and the need for cerebrospinal fluid shunt placement. *J Neurosurg Pediatr*. 2015;16(6):613-620. doi:10.3171/2015.7.PEDS15336

33. Geerdink N, Cuppen I, Rotteveel J, Mullaart R, Roeleveld N, Pasman J. Contribution of the corticospinal tract to motor impairment in spina bifida. *Pediatr Neurol*. 2012;47(4):270-278. doi:10.1016/j.pediatrneurol.2012.06.010

34. Bartonek A, Saraste H. Factors influencing ambulation in myelomeningocele: a cross-sectional study. *Dev Med Child Neurol*. 2001;43(4):253-260. doi:10.1017/S0012162201000482

35. Bartonek A, Saraste H, Samuelsson L, Skoog M. Ambulation in patients with myelomeningocele: a 12-year follow-up. *J Pediatr Orthop*. 1999;19(2):202-206. doi:10.1097/01241398-199903000-00013

36. 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

37. Findley TW, Agre JC, Habeck RV, Schmalz R, Birkebak RR, McNally MC. Ambulation in the adolescent with myelomeningocele, I: early childhood predictors. *Arch Phys Med Rehabil*. 1987;68(8):518-522.

38. Steinhart S, Kornitzer E, Baron AB, Wever C, Shoshan L, Katz-Leurer M. Independence in self-care activities in children with myelomeningocele: exploring factors based on the International Classification of Function model. *Disabil Rehabil*. 2018;40(1):62-68. doi:10.1080/09638288.2016.1243158

39. Schoenmakers MA, Uiterwaal CS, Gulmans VA, Gooskens RH, Helders PJ. Determinants of functional independence and quality of life in children with spina bifida. *Clin Rehabil*. 2005;19(6):677-685. doi:10.1191/0269215505cr865oa

40. Kabagambe SK, Chen YJ, Vanover MA, Saadai P, Farmer DL. New directions in fetal surgery for myelomeningocele. *Childs Nerv Syst*. 2017;33(7):1185-1190. doi:10.1007/s00381-017-3438-6