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Postoperative Ultrasound as a Predictor of Newborn Function and Ambulation after Open Fetal Myelomeningocele Repair

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Neural tube defect · Myelomeningocele · Fetal surgery · Prognosis · Neonatal outcome

Abstract
Objective: Function of the lower extremities after prenatal myelomeningocele (MMC) repair is best assessed with ambulatory function at 30–36 months of age, but parents often ask about function before this milestone. Lower extremity movement can be assessed by ultrasound (US) and at the newborn exam (NE), but correlation between US, NE, and ambulation is not firmly established. ***Methods:*** This was a retrospective correlation study of fetuses that underwent open prenatal MMC repair at SSM Cardinal Glennon Fetal Care Institute, St. Louis, MO, between January 2011 and June 2017. Movement at the ankles, knees, and hips was assessed by US after open repair on postoperative days (PODs) 0–5 and at 32 weeks gestation. NE was performed by physical therapy or neurosurgery within the first month of life, and pediatric follow-up between 30 and 36 months of age was obtained to document ambulation. ***Results:*** Forty-two fetuses were included. Joint movement seen on US varied by POD: it was present on POD 1 in 7% of fetuses and 62% by POD 5. Degree of ventriculomegaly, lesion level, and lesion length did not have a significant effect on US, NE, or ambulation. Knee movement on POD 3 correlated with knee movement at NE ($k = 0.58$, $p < 0.01$), but only later knee movement correlated with ambulation ($k = 0.28$–0.46, $p = 0.01$). Hip movement at 32 weeks was the only single joint assessment that correlated with NE and ambulation ($k = 0.45$ and 0.46, $p = 0.03$ and 0.01, respectively). ***Conclusion:*** Lower extremity movement increases between POD 1 and POD 5 in fetuses after open fetal MMC repair. Knee and hip movement on US at 32 weeks correlates with ambulation at 30–36 months. These data may inform counseling, and direct therapy and spark prospective investigations.

Introduction

Myelomeningocele (MMC) is the most common type of neural tube defect that is compatible with life [1]. It is characterized by the protrusion of neural elements through a bony defect of the spine. Although the incidence has decreased with maternal folic acid supplementation, it currently affects an estimated 5–10 pregnancies per 10,000 in

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the USA [2]. Liveborn infants have a death rate of approximately 10%, and long-term survivors have significantly impaired ambulation, various degrees of developmental delay, and bowel and bladder dysfunction [3].

Experimental and clinical evidence shows that the neurologic deficits associated with MMC are acquired early in development and progress in severity throughout pregnancy [4]. Movement in the lower limbs in fetuses with MMCs begins at 16–17 weeks gestation but may be lost as hydrocephalus, talipes, and hindbrain herniation worsen during gestation and even after birth [5–8]. Studies in animals demonstrate that prenatal coverage of a spina bifida-like lesion preserved neurologic function and improved hindbrain herniation [9–11]. Since the Management of Myelomeningocele Study (MOMS) findings, similar prenatal repair has become standard of care for eligible patients [12].

Lower extremity movement is the first outcome available to parents after prenatal repair of MMC. Ambulation at 30 months, with or without the use of assistive devices, is a major outcome for function throughout life, but is not immediately available to anxious parents. Ultrasound (US) can assess joint movement antenatally and has been compared to movement at birth. However, movement visualized by US has not been rigorously compared with neonatal findings, nor with ambulation after prenatal MMC repair.

The purpose of this study is to compare lower extremity movement seen by US with movement at the newborn exam (NE) and with ambulation at 30–36 months, in order to investigate US as a prognostic tool for parents, physicians, and therapists.

Materials and Methods

This was a retrospective cohort of open fetal MMC repairs at the SSM Cardinal Glennon Fetal Care Institute (FCI) between January 1, 2011, and June 33, 2017. It is FCI's standard protocol to perform US preoperatively, several hours after surgery, and every day until discharge to assess both maternal and fetal status. This US includes assessment of lower extremity movement, Doppler studies of fetal umbilical artery and vein, fetal middle cerebral artery peak systolic velocity, Doppler studies of the ductus venosus, transverse and sagittal planes of the MMC repair site, the deepest vertical pocket of amniotic fluid, and a view of the hysterotomy and maternal anterior and posterior cul-de-sac.

Maternal patients who were eligible for prenatal MMC repair were included in this study. During the study period, FCI used criteria from the MOMS trial, which included singleton pregnancy, lesion with an upper boundary located between T1 and S1, hindbrain herniation, a gestational age of 19 weeks 0 days to 25 weeks 6 days at consent, a normal karyotype, and a maternal age of at least 18 years. As in the MOMS trial, exclusion criteria included fetal anomaly unrelated to MMC, severe kyphosis, short cervix, previous preterm birth, placental abruption, a BMI of 35 or greater, and contraindication to surgery, including previous hysterotomy in the active uterine segment. Women undergoing MMC repair were eligible for this study, but MMC patients were able to decline participation. Importantly, women who were unable to receive the needed amount of ultrasounds or whose neonatal records did not become available were excluded from the study.

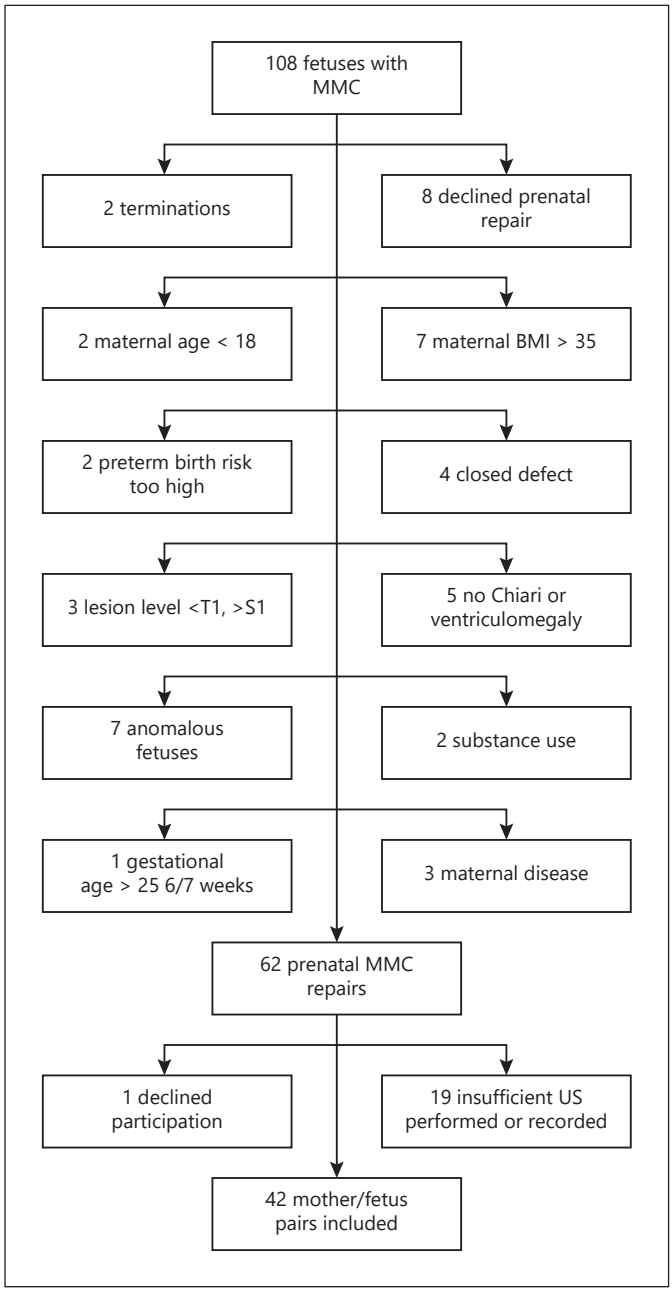

Fig. 1. Study flow diagram. MMC, myelomeningocele; US, ultrasound.

The primary outcomes were lower extremity movement on US, movement on NE, and ambulation (with and without the use of assistive devices). Secondary outcomes including types of assistive devices and freedom of ambulation were also collected.

Movement of ankles, knees, and hips was analyzed from inpatient US on the day of surgery or postoperative day (POD) 0 through POD 5. Maternal fetal medicine physicians performed all postoperative ultrasounds. All newborn exams were performed by a physical therapist or neurosurgeon within the first month of life. Results of these exams were abstracted from medical records by 2 clinical reviewers. Records from pediatric providers were sought to confirm 30- to 36-month outcomes for all study participants, including the freedom of ambulation (freely ambulating indoors, running or jumping, or only with assistive devices such as wheelchairs, walkers, crutches, or braces).

The study was approved by the St. Louis University Institutional Review Board on October 24, 2016, and again in 2019.

The primary outcomes of movement exist along a spectrum from very weak to strong and functional; similarly, ambulation varies from maximum assistance indoors to freely running on irregular terrian. Despite these variations, movement and ambulation were considered as categorial variables for the purposes of statistical analysis – any movement was counted as movement and any patient determined to be clinically ambulatory by pediatric teams was counted as ambulatory, even if occasional use of a wheelchair was required. To add resolution to these categories, data regarding lesion level, ventriculomegaly, and assistive devices were analyzed.

Cohen's kappa coefficients and z-scores were calculated to assess the agreement of US, NE, and ambulation, treating each of these assessments as "raters" rather than the individual providers performing the assessments. χ^2 tests or Fisher's exact tests were also utilized to compare proportions of normally distributed data. A p value of 0.05 was deemed significant.

Results

108 women were referred to FCI for evaluation of MMC between January 2011 and June 2017. Forty-six were excluded (see Fig. 1), and 62 women underwent prenatal MMC repair according to the MOMS criteria. One MMC repair patient declined participation in ongoing pediatric follow-up studies, and 19 women were excluded for insufficient ultrasounds performed according to the study protocol. The most common reason for failure to adhere to the FCI US schedule was delivery at a facility out of state. Forty-two of the patients who received MMC underwent sufficient ultrasounds with records available for review.

Demographic information is summarized in Table 1. Apart from race, the study group was comparable to the metropolitan population of St. Louis. The patient population was similar to the MOMS population in gestational age at diagnosis, suspected level of lesion, and delivery timing. The mean lateral ventricle diameter was 12.7 millimeters (mm), and ventriculomegaly greater than or equal to 15 mm was seen in 33% of fetuses (range 15–28 mm).

Table 1. Baseline characteristics and for 42 mother/fetus pairs

Age at diagnosis/consult	27±4.7
Race	
Caucasian	39 (95)
African-American	2 (5)
Parity	
Nulliparous	16 (39)
Parity ≥2	8 (20)
History of indicated preterm birth	1 (2)
Gestational age at initial consultation	21 6/7±1 2/7
Level of lesion	
Thoracic	2 (5)
Highest L1–L3	23 (55)
Highest L4–L5	15 (36)
Length of lesion (in segmental levels)	5.7±1.6
Gestational age at open prenatal repair	24 4/7±1 0/7
Gestational age at delivery	34 6/7±2 6/7
Ventriculomegaly ≥15 mm	14 (33)

Data are presented as mean ± standard deviation or n (%). Either ventricle could be greater than 15 mm. mm, millimeters.

Table 2. Selected outcomes for 42 fetuses after open fetal MMC repair

Movement on US	
POD 0	3 (7)
POD 1	9 (21)
POD 2	18 (43)
POD 3	23 (55)
POD 4	24 (57)
POD 5	26 (62)
32 weeks gestation age	32 (76)
Ambulation	
Any ambulation	35 (83)
Freely in home	23 (55)
Running and jumping	6 (14)
With assistive devices	23 (55)
Device type	
Wheelchair	11 (26)
Walker	16 (38)
Crutches	1 (2)
Braces	38 (90)

Data are presented as n (%). Responding parents could reply to use of more than one assistive device; there was particular overlap of braces with other devices. MMC, myelomeningocele; US, ultrasound; POD, postoperative day.

Table 3. Lower extremity movement and ambulation among fetuses grouped by lesion level and degree of ventriculomegaly

Variable	US movement	NE movement	Ambulation
Highest level of lesion			
Thoracic	1/2 (50)	2/2 (100)	1/2 (50)
L1–L3	17/23 (74)	21/23 (91)	22/23 (96)
L4–L5	13/15 (87)	14/15 (93)	12/15 (80)
p values	0.56	0.87	0.17
Ventriculomegaly			
<15 mm	19/27 (70)	22/27 (82)	21/27 (78)
≥15 mm	12/14 (86)	14/14 (100)	13/14 (93)
p values	0.28	0.09	0.22

Data are presented as *n* (%), and *p* values reflect χ^2 tests. Denominators in lesion level and degree of ventriculomegaly reflect the subgroups denoted by the row label (e.g., of the 2 patients with thoracic MMC, half had movement on US and half ambulated). US, ultrasound; NE, newborn exam; MMC, myelomeningocele; mm, millimeters.

Selected outcomes are displayed in Table 2. Movement on US was rare immediately after surgery (POD 0 to POD 2; see Table 2). Any joint movement on US was present on POD 1 in 7% of fetuses, 62% by POD 5, and 76% at 32 weeks. No joint movement correlated with NE or ambulation on POD 0 or POD 1.

Ambulation was achieved by 83% of patients, with 55% ambulating freely at home and a smaller number running and jumping. The majority of patients used assistive devices, with braces and walkers being the most commonly used (Table 2).

Degree of ventriculomegaly and level of lesion did not modify movement seen on US, movement at NE, or ambulation at 30 months. These data are summarized in Table 3, and analysis joint by joint was not different from a summation of all types of joint movement and all types of ambulation. Length of lesion in spinal segments was also not different between groups with each finding (5.7 ± 1.8 in those with movement on US, 5.7 ± 1.6 with movement at NE, and 5.9 ± 1.6 in those able to ambulate); and longer lesions were not associated with fewer movements or lower rates of ambulation.

Movement at either ankle on US from POD 2 to 32 weeks correlated with movement of the ankle at NE, but did not correlate with ambulation (see Table 4). For example, on POD 3, movement in both ankles had a strong relationship with NE ($k = 0.71$, $p < 0.001$), but this had no relationship with ambulation ($k = 0.01$, $p = 0.33$). Knee movement on POD 3 correlated with knee movement at NE ($k = 0.58$, $p < 0.01$), but not with ambulation; however, later knee movement (for instance, POD 5 and 32 weeks) correlated with ambulation, but not with NE ($k = 0.28$–0.46, $p = 0.01$). The only single joint assessment by US that correlated with both NE and ambulation was the hip at 32 weeks ($k = 0.45$ and 0.46, $p = 0.03$ and 0.01, respectively).

Discussion/Conclusion

This paper shows that movement detected by US after open fetal MMC repair at the knee and hip at 32 weeks correlates with ambulation at 30–36 weeks. In addition, movement (or the absence of movement) on US in the first few days after surgery has no bearing on future outcomes; the ankle is not predictive of ambulation despite a dramatic association with NE. Degree of ventriculomegaly, lesion level, and lesion length do not appear to have a strong influence on NE or ambulation.

Previous literature outlines a "spinal shock" which occurs after postnatal repair of MMC. Our paper is consistent with significantly less movement in the early postoperative period; however, the assessment of true "spinal shock" after prenatal MMC repair is confounded by the fact that the magnesium sulfate administered perioperatively can cause decreased fetal movement.

Previous literature demonstrates that movement can be characterized in fetuses with MMCs by US and that fetuses with MMCs can have movement present although it can be lost if surgery is not performed ("two-hit hypothesis" of exposure of nerve tissue to amniotic fluid or physical damage secondary to hydrocephalus) [4, 13, 14]. Our findings preliminarily show a reversal in this process, with increasing prevalence of movement throughout gestation.

This study's strengths include a relatively complete data set in patients seen at SSM Cardinal Glennon Fetal Care Institute and a single surgical team. Weaknesses include that this study period occurred during development of database integrity and surgical technique and that this retrospective design is necessarily limited by missing data.

US can be used as a short-term prognostic tool to approximate expected movement at birth. US of the knee and hip at 32 weeks gestation may be helpful in planning therapy for children after open fetal MMC repair. Future research should confirm these findings in additional samples in a prospective fashion and assess other factors (duration of exposure to amniotic fluid, fetoscopic vs. open approach, and graft type) that may impact lower extremity function.

Table 4. Correlation of US with newborn exam and ambulation for 42 fetuses/neonates

Joint	Timing	Correlation with newborn exam		Correlation with ambulation	
		kappa (z-score)	*p* value	kappa (z-score)	*p* value
Right ankle	POD 0	0.22 (0.94)	0.35	NC	NC
	POD 1	0.19 (1.70)	0.09	0.01 (0.31)	0.76
	POD 2	0.34 (2.44)	**0.01**	0.04 (0.67)	0.50
	POD 3	0.71 (3.4)	**<0.001**	0.10 (0.98)	0.33
	POD 4	0.66 (2.97)	**<0.01**	0.17 (1.29)	0.2
	POD 5	−0.18 (−0.66)	0.51	0 (0)	1.0
	32 wks	0.68 (3.28)	**<0.01**	0.19 (1.5)	0.13
Left ankle	POD 0	0.33 (1.1)	0.27	NC	NC
	POD 1	0.13 (1.37)	0.17	0.003 (0.21)	0.83
	POD 2	0.4 (2.44)	**0.01**	0.04 (0.67)	0.5
	POD 3	0.71 (3.4)	**<0.001**	0.095 (0.98)	0.33
	POD 4	0.66 (2.97)	**<0.01**	0.17 (1.29)	0.2
	POD 5	0.26 (0.98)	0.326	NC	NC
	32 wks	0.78 (3.71)	**<0.0001**	0.19 (1.5)	0.13
Right knee	POD 0	0.33 (1.1)	0.273	NC	NC
	POD 1	0.112 (1.29)	0.198	0.08 (0.93)	0.35
	POD 2	0.3 (1.72)	0.08	0.27 (1.72)	0.09
	POD 3	0.58 (2.67)	**<0.01**	0.27 (1.66)	0.10
	POD 4	0.39 (1.81)	0.07	NC	NC
	POD 5	NC	NC	0.46 (2.58)	**0.01**
	32 wks	0.33 (1.62)	0.1	0.28 (2.5)	**0.01**
Left knee	POD 0	0.33 (1.1)	0.27	NC	NC
	POD 1	0.09 (1.13)	0.26	0.01 (0.39)	0.7
	POD 2	0.35 (1.95)	0.05	0.1 (1.03)	0.31
	POD 3	0.58 (2.67)	**<0.01**	0.27 (1.72)	0.09
	POD 4	0.39 (1.81)	0.07	0.27 (1.66)	0.10
	POD 5	NC	NC	NC	NC
	32 wks	0.45 (2.17)	0.03	−0.06 (−0.32)	0.75
Right hip	POD 0	0.33 (1.1)	0.27	NC	NC
	POD 1	0.11 (1.25)	0.21	0.01 (0.39)	0.7
	POD 2	0.19 (1.0)	0.32	−0.10 (−0.75)	0.5
	POD 3	−0.13 (−0.61)	0.54	−0.09 (−0.35)	0.73
	POD 4	−0.08 (−0.43)	0.67	−0.06 (−0.25)	0.8
	POD 5	NC	NC	0 (0)	1.0
	32 wks	0.33 (1.57)	0.12	0.46 (2.51)	**0.01**
Left hip	POD 0	0.33 (1.1)	0.27	NC	NC
	POD 1	0.08 (1.06)	0.29	0.01 (0.39)	0.7
	POD 2	0.19 (1.0)	0.32	−0.10 (−0.75)	0.5
	POD 3	−0.08 (−0.42)	0.68	−0.06 (−0.24)	0.81
	POD 4	−0.08 (−0.43)	0.67	−0.06 (−0.25)	0.80
	POD 5	NC	NC	NC	NC
	32 wks	0.45 (2.11)	**0.03**	0.46 (2.51)	**0.01**

Data are presented as Cohen's kappa and 95% confidence interval. Ambulation refers to any ambulation, with and without devices. US, ultrasound; wks, weeks; NC, not calculated due to significant missing data; POD, post-operative day.

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Statement of Ethics

This research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved as protocol 29,960 by the St. Louis University Institutional Review Board on October 24, 2016, and again on April 23, 2019, assurance number FWA00005304. All subjects gave their written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.P. and A.F. conceived the work. C. Buskmiller and C.P. reviewed records and performed data analysis. C. Buskmiller wrote the manuscript. C. Buskmiller, C. Buchanan, C.P., and A.F. contributed to the final version of the data and manuscript and approve of it in its final form.

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