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Fractional Limb Volume in Spina Bifida Fetuses as an Assessment Tool for Postnatal Ambulation

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Keywords

Fractional limb volume · Myelomeningocele · Ambulation · Motor function · Prenatal repair · Fetal tissue mass biometry

Abstract

Background: Prenatal fractional limb volume (FLV) can be used to assess muscle atrophy in fetuses with myelomeningocele. ***Objective:*** We hypothesize that FLV in fetal myelomeningocele (fMMC) repair is different from postnatal repair (PNR). Assessing intrauterine muscle development can predict ambulation. ***Methods:*** A prospective observational study was performed from July 2012 to April 2016. Demographics, clinical outcomes, and FLV of the fetal thigh were assessed by ultrasound. Ambulation videos were collected from patients over 30 months of age. FLV was compared between the fMMC and PNR groups and between ambulators and non-ambulators. Two-sample *t* test, ANOVA, Spearman's rho correlation, and Bland-Altman plots were used for analysis. A p value <0.05 was used for statistical significance. ***Results:*** Fifty-nine patients were included, 24 had fMMC and 35 had PNR. Videos were obtained in 47 cases (73%). There was no difference in baseline demographics between the groups. There was no significant change in the fMMC group between the FLV at initial presentation and the repeat at 34 weeks gestation (54.5 ± 28.2 and 62.2% ± 16.4; p = 0.6). In contrast, the FLV in the PNR decreased between the initial evaluation and the repeat at 34 weeks (54.1 ± 27.7 to 35.8 ± 34.1%; p = 0.04). FLV at 34 weeks gestation was higher in the fMMC group as compared to the PNR group (62.2 ± 16.4 vs. 35.8 ± 34.1%; p = 0.02). There was no difference in FLV between ambulators and non-ambulators either at initial evaluation (p = 0.8) or at 34 weeks gestation (p = 0.6). ***Conclusion:*** Lower FLV in the PNR group compared to fMMC may suggest in utero muscle atrophy. No correlation was seen between FLV and subsequent ambulation; however, future larger studies may be needed.

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Introduction

Spina bifida is a congenital anomaly of the central nervous system associated with neurological complications, loss of bowel and bladder function, and deterioration of lower extremity motor control. There are approximately 1,500 babies born with spina bifida each year in the USA [1]. Myelomeningocele is the most severe form of spina bifida or open neural tube defects (ONTD) in which there is a defect in the vertebral column with a sac-like protrusion of the meninges and spinal cord.

With advances in the available medical and surgical interventions, the long-term outcomes have improved. The Management of Myelomeningocele Study (MOMS) trial demonstrated the benefits of in utero repair of fetal myelomeningocele (fMMC) compared to postnatal repair (PNR), resulting in decreased need for shunt placement at 12 months and better outcomes in motor and intellectual development at 30 months [2].

In the absence of hydrocephalus, children affected by spina bifida may achieve similar educational goals as their unaffected peers [3]. Roach et al. [4] found that 42% of enrolled patients had normal IQs. The most important considerations for the patient's quality of life is urinary/bowel continence and the ability to ambulate, with the latter being a predictor of occupational potential [5]. It has also been shown that the ability to ambulate at 30 months significantly decreases parental stress and the impact on the family unit [6]. Thus, being able to predict the extent of future motor function would be essential in determining longitudinal care for the child. Currently, the level of lesion and presence of in utero fetal limb movements have been used to predict postnatal ambulation [7–9].

Fractional limb volume (FLV) is a validated sonographic tool that uses three-dimensional (3D) ultrasound analytical principles, where a constant central portion or "fraction" (50%) of the upper lower fetal extremity is used to estimate the entire extremity volume [10]. FLV has been evaluated in the assessment of fetal weight and gestational age (GA)-based normative values have been reported. It remains unknown if the decreased FLV in utero may be used as an indicator of muscle atrophy.

In this study we sought to determine if there was a difference in the FLV of patients that underwent fMMC repair compared to PNR. In addition, we sought to determine if the FLV could be used to predict ambulation in infants affected by spina bifida.

Materials and Methods

A prospective observational study was conducted at McGovern Medical School at the University of Texas Health Science Center and the Fetal Center at Children's Memorial Hermann Hospital, Houston, TX, USA, from July 2012 to April 2016. This study was approved by the Institutional Review Board (IRB No. HSC-MS-12-0622).

Patients with suspected spina bifida referred to our center underwent an extensive evaluation, which included a comprehensive ultrasound using 3D imaging to determine the bony level of lesion as well as prenatal MRI to determine the presence and level of cerebellar tonsillar herniation (Chiari II malformation). Leg movement was defined using real-time ultrasound to note flexion and extension movements of the hips and knees. The presence of talipes was also assessed.

Once the diagnosis of an ONTD was confirmed all women were offered enrollment in the study. Demographic information including age, race, GA at initial evaluation, and GA at delivery were recorded. Other variables that were assessed included the level of the spinal lesion, type of the spinal lesion (myeloschisis vs. myelomeningocele), head circumference, ventricular size, presence or absence of Chiari II malformation, and level of herniation if present, presence or absence of other CNS malformations, presence of fetal lower extremity movement, presence of lower extremity deformations, candidacy for antenatal repair, presence or absence of intrauterine growth restriction, and the presence or absence of other congenital malformations.

The FLV measurements were obtained as described by Lee et al. [10]. Images were obtained using the curved abdominal transducers (RAB 6D, RAB 2-5D; Voluson VE8 Expert; GE Healthcare, Milwaukee, WI, USA). The image volumes were saved for analysis offline. Depth and magnification were adjusted so that the fetal thigh filled two-thirds of the screen. The femur that was located anteriorly or closer to the maternal abdominal wall was selected. Fifty percent of the thigh or femoral diaphyseal length was used to calculate the FLV. Electronic cursors were placed at each end of the femoral diaphysis. Volumes were obtained at five equidistant slices that were located at the mid portion of the femoral diaphysis (Fig. 1). FLVs were calculated using the commercially available software (4D View 5.0; GE Healthcare). The software automatically calculates FLVs after each of the five slices are manually traced from a transverse view of the extremity. Each measurement was performed in triplicate and the average was recorded. The average was then converted to a percentile compared to the normal FLV at the same GA [10]. FLV was measured at the initial evaluation and then serially with each subsequent ultrasound. FLV was compared between the fMMC and PNR groups. In each group it was compared longitudinally between that obtained at the initial presentation and that obtained at 34 weeks gestation.

Functional assessment at 30 months age was accomplished by asking the parents to assess the ability of the children to ambulate independently or with the assistance of devices. The families provided a 1-min video clip of the child's ambulation using a mobile phone device. A single examiner who was blinded to the group assignment (fMMC or PMR) evaluated these videos. Ambulation was defined as none (wheelchair bound) or ambulation with or without assistance. Aids that were used to assist with ambulation included walkers and braces. FLV between the ambulators and non-ambulators was analyzed.

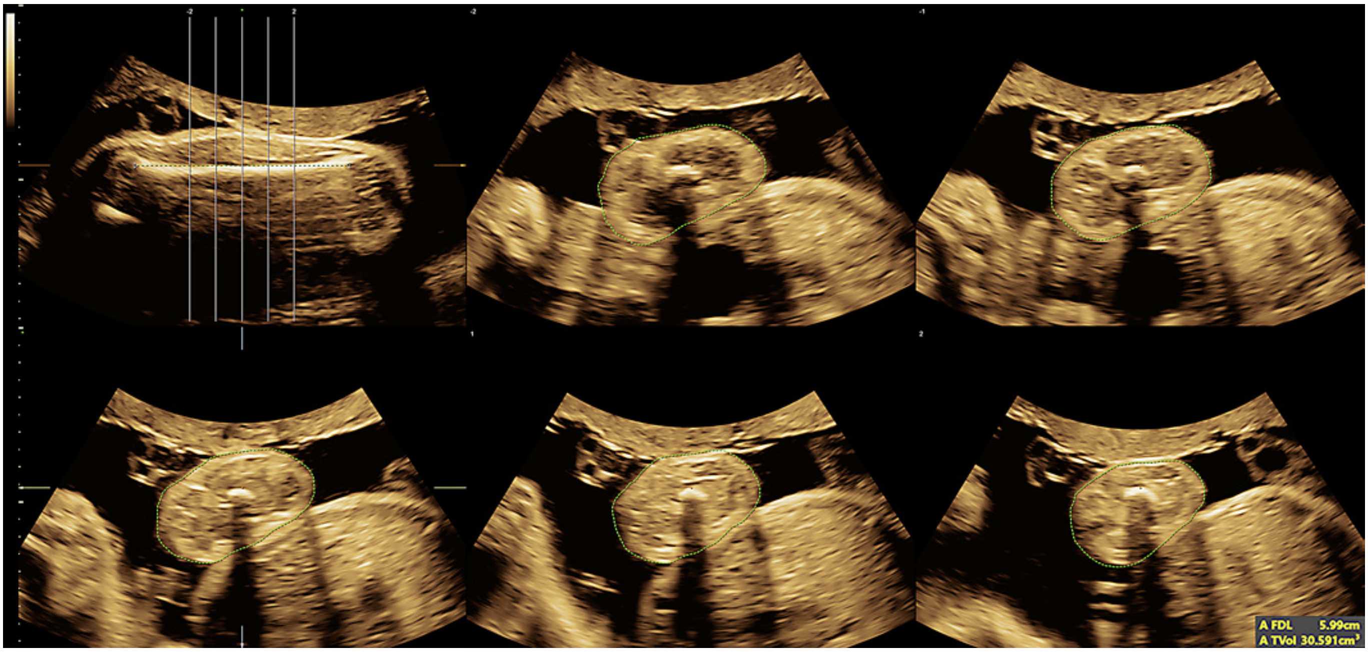

Fig. 1. Ultrasound image demonstrating the measurement of fetal thigh volume. The image in the upper left corner is the entire thigh with 5 lines or points of cross-section, where the volumes are measured. The remaining 5 images demonstrate how the volumes are outlined. At the end of the 5th image, the in-built thigh volume software calculates the overall volume.

A 2-sample *t* test and ANOVA were used to assess the baseline characteristics between groups. Spearman's rho correlation was used to assess the correlation between ambulation and FLV percentile at different GAs. Bland-Altman plots were used to determine the 95% limit of agreement (LOA) and bias for a single examiner and between examiners. A *p* value <0.05 was considered statistically significant.

Results

Seventy-five patients were enrolled in the study from July 2012 to April 2016. Twenty-six patients had fMMC repair and 49 patients had PNR (Fig. 2).

Of the fMMC group, 1 patient withdrew from the study and there was 1 neonatal demise. Ambulation videos were obtained in 23 of the remaining 24 patients (95.8%) after 30 months of age. In the PNR group, 3 patients opted to terminate the pregnancy, there was 1 neonatal demise and 5 withdrew from the study. Five additional patients were excluded from the PNR group due to poor ultrasound image quality resulting in the inability to analyze the fetal limb volume. Videos of ambulation after 30 months were obtained on 24 of the remaining 35 patients (68.5%).

There was no significant difference in age, gravidity, parity, GA at initial evaluation, and GA at delivery between the fMMC and PNR groups (Table 1). The fMMC group was more likely to have a higher level of lesion compared to the PNR group ($p < 0.001$). Only 1 patient in each group did not have leg movement at initial evaluation.

There was no significant change in the fMMC group between the FLV at initial presentation and the repeat at 34 weeks gestation (54.5 ± 28.2 and 62.2 ± 16.4%; $p = 0.6$; Fig. 3). In contrast, the FLV in the PNR decreased between the initial evaluation and the repeat at 34 weeks (54.1 ± 27.7 to 35.8 ± 34.1%; $p = 0.04$). FLV at 34 weeks gestation was higher in the fMMC group as compared to the PNR group (62.2 ± 16.4 vs. 35.8 ± 34.1%; $p = 0.02$; Fig. 4). There was no difference in FLV between ambulators and non-ambulators either at initial evaluation ($p = 0.8$) or at 34 weeks gestation ($p = 0.6$; Fig. 5). There was also no difference in the change in FLV from initial to final measurement between ambulators and non-ambulators ($p = 0.3$, the average change in FLV in ambulators was 34.3 and in non-ambulators was 35.1; Fig. 6).

Spearman's rho was calculated to assess the correlation between FLV percentile at each GA and ambulation in

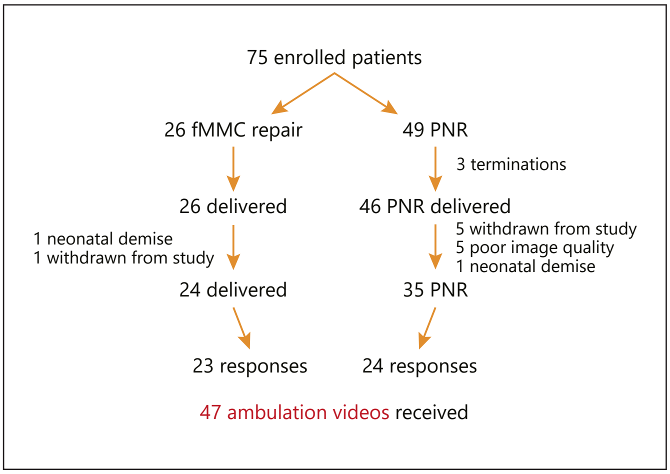

Fig. 2. Flow diagram for the participants of this study. fMMC, fetal surgery; PNR, postnatal repair.

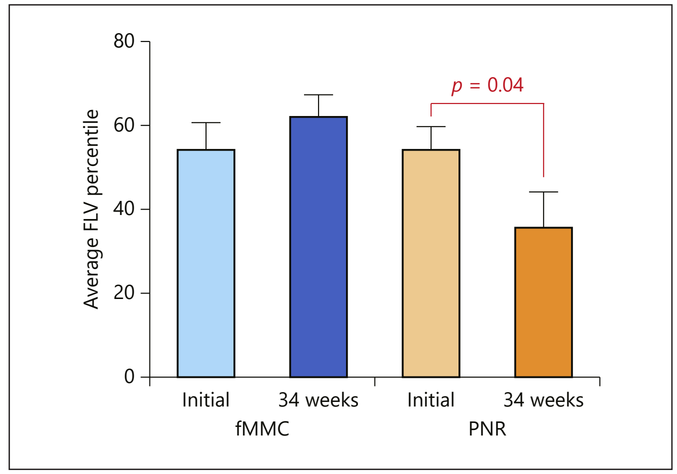

Fig. 3. Assessment of FLV at initial and 34 weeks gestation in both the fetal surgery (fMMC) and PNR groups. $p = 0.6$ in fMMC vs. 0.04 in PNR.

Table 1. Characteristics of the fMMC and PNR groups

	fMMC ($n = 23$)	PNR ($n = 24$)	p value
Age, years	27±5.8	27±5.7	0.05
Gravida	2 (1–5)	2 (1–5)	0.74
Para	2 (0–4)	1 (0–3)	0.96
GA at initial evaluation, weeks	23.5±2.1	23.5±2.1	0.28
Level of lesion			
Thoracic	3 (13)	1 (4.1)	0.001
L1–L2	9 (39.1)	3 (12.5)	
L3–L4	9 (39.1)	5 (20.8)	
L5–S1	1 (8.7)	15 (62.5)	
Lesion level L3 or lower on ultrasound	10 (43.5)	20 (83.4)	0.009
Myelomeningocele	14 (60.9)	19 (79.2)	0.08
Myeloschisis	9 (39.1)	5 (20.8)	0.08
No leg movement (no movement at the hip or knee)	1	1	
GA at delivery, weeks	35.8±2.6	36.1±2.4	0.3
Postnatal ambulation			
Wheelchair	2 (8.6)	8 (33.3)	0.04
Walker	12 (52.2)	5 (20.8)	
Ambulating	9 (39.1)	11 (45.8)	

Data are presented as the mean ± SD, median (range), or n (%). fMMC, fetal surgery; PNR, postnatal repair; GA, gestational age.

each group. In the fMMC group, the correlation between FLV percentile at initial evaluation to ambulation was −0.03 ($p = 0.8$), and no correlation seen at 28 weeks and at 34 weeks was 0.53 ($p = 0.11$). For the PNR group, correlation between the FLV percentile at initial evaluation to ambulation was 0.22 ($p = 0.38$), at 28 weeks was −0.16 ($p = 0.6$), and at 34 weeks was −0.42 ($p = 0.13$).

The number of patients that were able to ambulate at 30 months in the fMMC group was 21 (91.3%) compared to 16 (66.6%) in the PNR group. In the fMMC group, 2 (8.6%) patients were wheelchair bound and did not ambulate. Of those who were able to ambulate, 12 (52.2%) used a walker and 9 (39.1%) patients were either walking independently without any assistance or with the use of

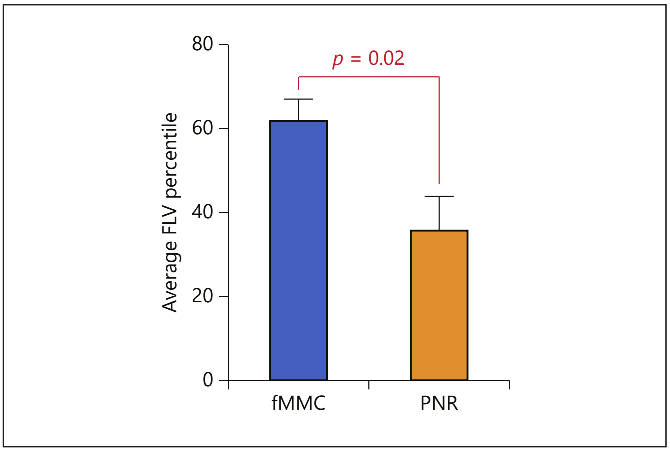

Fig. 4. Comparison of FLV at 34 weeks in the fetal surgery (fMMC) and PNR groups ($p = 0.02$).

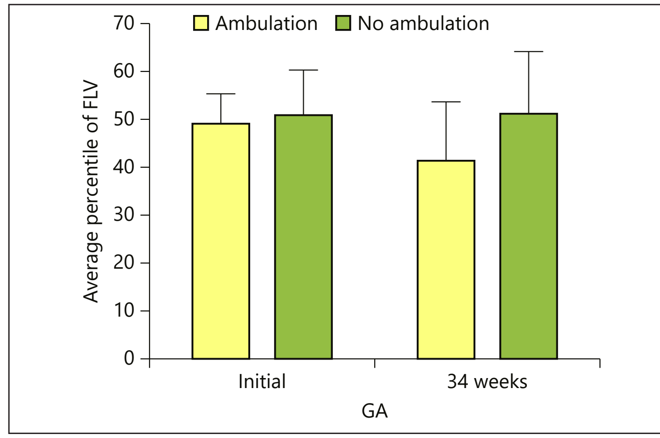

Fig. 5. Comparison of FLV in the patients with ambulation versus no ambulation ($p = 0.8$ at initial evaluation; $p = 0.6$ at 34 weeks).

some assistance with braces. In the PNR group, 8 (33.3%) patients were wheelchair bound and did not ambulate. The patients that were able to ambulate included 5 (20.8%) using walkers and 11 (45.8%) patients who were either walking independently or with the help of braces.

Bland-Altman plots were used to assess the reproducibility of the FLV measurements. Two observers (R.D., M.H.) reviewed images of the thigh volume on 20 random patients for this assessment. Satisfactory inter- and intra-observer bias and agreement were noted (Fig. 7). The mean inter-observer bias ± SD and agreement was –0.34 ± 0.94 (95% LOA, –2.19 to 1.51). The intra-observer bias and agreement was –0.47 ± 3.08 (95% LOA, –6.51 to 5.58).

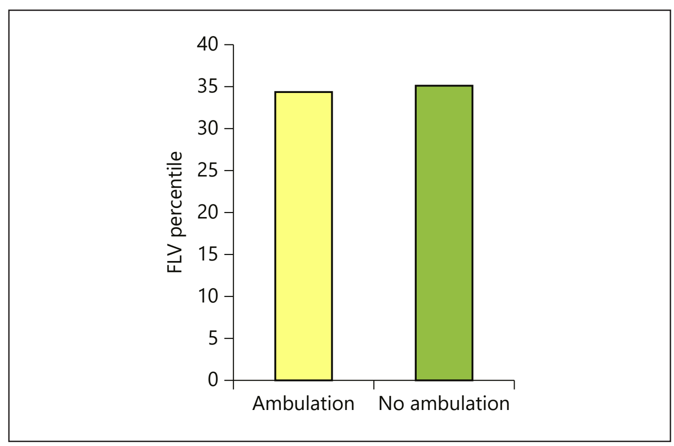

Fig. 6. Comparison of change in FLV in the patients with ambulation versus no ambulation ($p = 0.3$, average change for ambulators was 34.3, for non-ambulators the average change was 35.1).

Discussion

In our study, there was no difference in the FLV at initial evaluation, performed at less than 26 weeks gestation, between the fMMC and PNR groups. There was however a significant difference at 34 weeks gestation, with a lower FLV in the PNR group. In the PNR group, there was a decrease in the FLV at 34 weeks compared to initial evaluation. This decrease was not seen in the fMMC group of patients. FLV changes, however, were not predictive of the ability to ambulate at 30 months of age in either group.

Patients with ONTDs have neurologic impairment of their lower extremities which affects the ability to ambulate. Muscle atrophy is commonly seen in varying types of neuromuscular disorders. This atrophy can be assessed by ultrasound in the postnatal period [11–13]. Studies in adults have shown that muscle atrophy below the affected level of lesion rapidly develops following acute spinal cord injuries. In animal studies the muscle volume can be reduced by as much as 70% in just a few weeks [14, 15]. Similarly, MRI studies evaluating muscle volumes of the lower extremities in patients immobilized following ankle fracture have shown a significant decrease of individual muscle volumes and total lower extremity volume following immobilization after a period of 6 weeks [16]. Neurologic insults during the fetal period, which is a crucial time in development, could result in atrophy of the muscles to

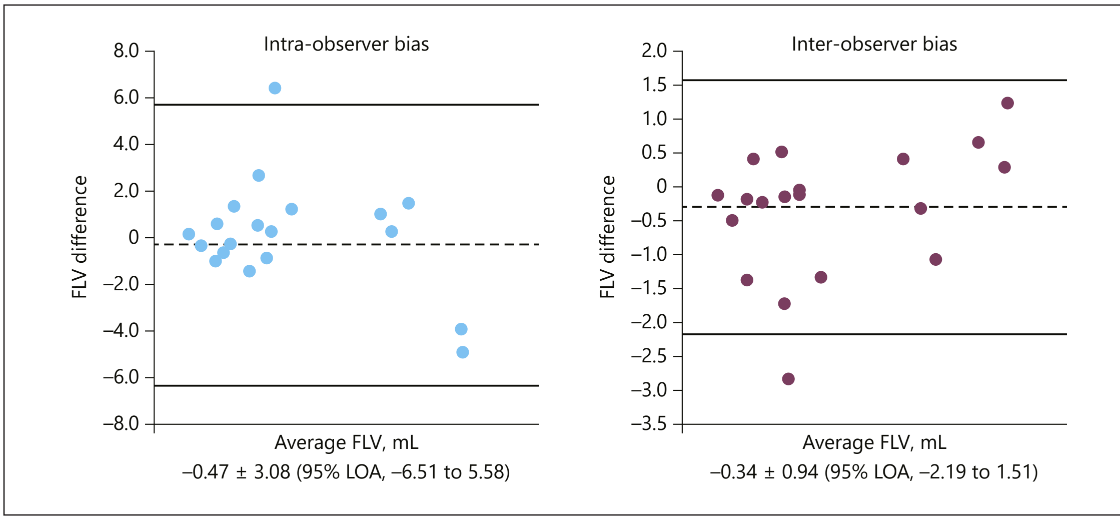

Fig. 7. Intra- and inter-observer variability for the measurement of the FLV. LOA, limits of agreement.

varying degrees. Prenatal assessment of this muscle atrophy could potentially be used as a predictor of postnatal motor functioning in fetuses affected by ONTDs.

3D ultrasound has been used to quantify soft tissue and assess limb volume. Earlier studies measured the entire extremity volume, which was time consuming [17, 18]. FLV is a sonographic tool that has been used to assess the fetal nutritional status. It is based on the 3D ultrasound principles, where only a fraction of the thigh volume is used to assess the entire thigh volume [10]. It can be done in a few minutes and is reproducible. Thigh volume includes both lean muscle mass and subcutaneous fat. The adipose tissue growth depends on intact sympathetic innervation. In case of neurologic damage, both the muscle and adipose tissue undergo atrophy and therefore the overall thigh volume decreases [19]. In fetal life there is a rapid increase in lean mass and subcutaneous fat in the third trimester [20, 21]. There are no studies assessing the effects on this growth in case of neurologic injury and disruption of the normal innervation of these tissues. Use of FLV in the assessment of the fetal thigh volume provides us with this information and helps assess for potential in utero muscle atrophy, which could then be a possible predictor of future motor control.

Several studies have sought to determine predictors of postnatal ambulation in cases of ONTDs. Farmer et al. [7] recently published the 30-month motor outcomes on all patients from the MOMS trial. The level of the lesion, lower extremity movement, especially at the hip and knee, and the absence of a sac covering the lesion were associated with the ability to ambulate independently. Carreras et al. [9] reported that the anatomic level of lesion was not accurate in predicting postnatal ambulation. Ultrasound assessment of lower extremity movement was better as a predictor of the ability to ambulate.

To our knowledge, there are no studies utilizing FLV as an assessment tool for postnatal ambulation in patients with ONTDs. We assessed FLV at the initial evaluation and then serially with each ultrasound until delivery. Since the average GA at delivery in the MOMS trial was 34 weeks for patients who underwent in utero MMC repair, we chose to use the thigh volume obtained closest to this GA for the final FLV for analysis.

In the fMMC group, 91% were able to ambulate at 30 months of age compared to only 66% in the PNR group ($p = 0.04$). This includes patients ambulating either with a walker or independently with or without the use of braces. When we looked only at patients who were able to ambulate independently, there was no difference between the groups (41% of the fMMC patients and 52% of the PNR group, $p = 0.5$). The MOMS trial and the follow-up assessment of these patients reported an increased ability to walk independently in the fetal surgery compared to PNR groups (42 vs. 21%, $p = 0.01$, and 44.8 vs. 23.9%, $p = 0.004$, respectively) [2, 7]. In our study, 62.5% of the patients in the PNR group had L5-S1 lesions compared to only 8.7% in the fMMC group. Based on this distribution, we would expect that fewer patients in the fMMC group would be able to ambulate, considering that the higher level of lesion would be associated with a poorer neurologic outcome. However, our overall rate of ambulation, including use of assistance was higher than expected.

Our study did not demonstrate any correlation between the average FLV percentile obtained at the initial evaluation or at 34 weeks gestation and postnatal ambulation. One of the limitations of our study was the small sample size. The response rate was lower in the PNR group. We speculate that there were poor postnatal outcomes in the PNR group such as an increased need for shunts, prolonged hospitalizations, and inability to ambulate, thereby resulting in an unwillingness to respond. Another limitation was the difficulty to interpret ultrasound images in the third trimester due to fetal positioning resulting in poorer image quality. This resulted in the inability to assess the FLV in 5 cases in the PNR group.

In conclusion, there is a significant decrease in FLV between fetal surgery and postnatal surgery fetuses at 34 weeks gestation. This would suggest in utero muscle atrophy in the PNR group. There was no correlation between FLV and ambulation; however, this may likely be due to our small sample size. Future larger studies are needed to assess for any correlation between in utero assessment of muscle atrophy and the ability to ambulate.

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Statement of Ethics

Subjects (or their parents or guardians) gave their written informed consent. The study protocol was approved by the committee on human research (IRB No. HSC-MS-12-0622).

Disclosure Statement

The authors have no conflicts of interest to declare.

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