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Contemporary Outcomes of a National Fetal Spina Bifida Surgery Service

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ABSTRACT

Objective: To assess contemporary outcomes of fetuses who underwent open fetal spina bifida surgery in Canada.

Methods: Our clinical program prospectively collected outcomes of all consecutive fetuses who underwent open fetal spina bifida closure at the Ontario Fetal Center in Toronto and who were at least 1 year of age at the time of postnatal follow-up. We gathered information on the need for hydrocephalus treatment, motor function, bladder function, as well as neurodevelopment (Ages and Stages Questionnaire and Bayley's scales of infant development). Developmental outcomes were categorized as "Typical Development," "Possible Delay," or "Significantly Delayed."

Results: Between 2017 and 2022, 41 fetuses underwent open fetal spina bifida closure. Twenty-four patients (58.5%) responded to the questionnaire at a median age of 46.5 months. Eight children (33.3%) required CSF diversion procedures. Bladder management included clean intermittent catheterization (43.5%), spontaneous voiding (34.8%), or both (21.7%), with 43.5% needing medication for overactive bladder. All patients could sit independently, with 50% walking outside and 50% crawling indoors. Among those walking outdoors (50%), 25% did so without orthotics or aid, 58.3% with orthotics, and 16.7% required additional walking aids. Most children demonstrated typical communication and problem-solving skills (79.2%), while gross motor development was significantly delayed in 91.7% of cases. Fine motor skills varied, with 56.5% showing typical development and 34.8% possibly experiencing delays.

Conclusions: This study showed a mixed developmental profile among patients who underwent open fetal spina bifida repair, consistent with the MOMs trial findings.

Summary

- What's already known about this topic?
  - Open spina bifida affects approximately 4.63 per 10,000 births globally and 150 fetuses annually in Canada.
  - It is characterized by an exposed spinal cord that leads to progressive injury, hydrocephalus, and hindbrain herniation; the MOMS trial showed that prenatal surgery improves motor function and reduces the need for ventriculo-peritoneal shunting.
- What does this study add?
  - This study provides follow-up data for infants who have undergone open fetal spina bifida closure at our center since 2017, confirming that the procedure can be successfully replicated outside the MOMs trial and offering insights into outcomes beyond the neonatal period.

1 | Introduction

Despite the availability of preventative interventions, open spina bifida still occurs in approximately 4.63 per 10,000 births globally and the condition is diagnosed in about 150 fetuses annually in Canada [1, 2]. In open spina bifida, the absence of a protective skin layer covering the spinal cord leaves the neural placode exposed to the uterine environment, rendering it vulnerable to progressive injury during pregnancy [3]. Additionally, leakage of cerebrospinal fluid from the lesion results in hindbrain herniation and secondary hydrocephalus [4]. Fetal intervention for spina bifida was proposed as secondary prevention to mitigate damage to the neural placode and reduce the incidence of hydrocephalus. The Management of Myelomeningocele Study (MOMS) confirmed the benefits of prenatal intervention, with lower rates of ventriculo-peritoneal shunting and better motor function being observed in fetuses operated on before birth [5, 6]. To many parents, the benefits of in-utero surgery outweigh the risks of preterm birth and maternal morbidity. As such, the uptake of fetal spina bifida surgery has increased worldwide, with now more than 40 centers offering this treatment [7, 8].

Our center started offering fetal spina bifida closure to Canadian patients in 2017, and our surgical protocol and early outcomes have been published previously [9]. We demonstrated that fetal spina bifida treatment could be replicated in experienced fetal therapy centers that had not participated in the seminal MOMS trial, with very comparable short-term results. However, more than short-term outcomes, prospective parents want information beyond the neonatal period. We have therefore been collecting medium-term follow-up on our patients and here describe outcomes of infants that have reached the age of at least 1 year.

2 | Methods

2.1 | Patient Population

This cross-sectional study reviewed the medium-term outcomes of all consecutive fetuses who underwent open prenatal surgery for spina bifida at the Ontario Fetal Center, Toronto, Canada, from the initiation of the program in 2017 until October 2022 to ensure that each case had a minimum of 1 year of postnatal follow-up. We prospectively collected follow-up information in these pregnancies for clinical audit and quality control. Local patients are followed through the multidisciplinary spina bifida clinic at Holland Bloorview Kids Rehabilitation Hospital, the developmental clinic at Mount Sinai Hospital and the neurosurgical service at the Hospital for Sick Children. Patients that are geographically distant from Mount Sinai Hospital are followed through their local tertiary programs. Information on these patients was collected directly from the patient via email, and in the absence of response, by phone, in an attempt to obtain as complete outcomes as possible as previously described by others [10]. This study was approved by the REBs at Mount Sinai Hospital, The Hospital for Sick Children and Holland Bloorview through Clinical Trials Ontario (CTO Project ID 1660).

2.2 | Data Collection

Medical records were screened to extract maternal and fetal baseline characteristics, including maternal age at surgery, gestational age (GA) at surgery, GA at delivery, fetal sex, spina bifida lesion type, and upper spinal level of the defect. Postnatal height, weight and head circumference percentiles were calculated according to Center of Disease Control and Prevention (CDC) charting system [11].

For all patients, we collected information on survival, need for cerebrospinal fluid (CSF) diversion procedures, seizures, motor function, orthopedic procedures, feeding status, bowel function, urological function and engagement in physical, occupational, and speech therapy sessions. Neurodevelopmental status was assessed by the Bayley Scales of Infant and Toddler Development (3rd edition) (Bayley-III) at the corrected age of 2 years for those who were assessed at our centers [12]. Standard scores on the Bayley-III scales range from above average (2 to 1 SD, score 116–130), average (1 to −1 SD, score 85–115), below average (−1 to −2 SD, score 84–70) and well below average (< −2 SD, scores < 70) [13].

Additionally, all parents were asked to complete the age-appropriate Ages and Stages Questionnaire, Third Edition (ASQ-3) [14]. ASQ-3 is a standardized developmental screening tool devised to evaluate children's developmental progress across various age brackets. It comprises a series of questions addressing fundamental developmental domains, including communication, gross and fine motor skills, problem-solving, and personal-social skills. Caregivers or parents complete the questionnaire based on their observations of the child's behaviors and abilities. ASQ-3 aids in the early identification of potential developmental delays or concerns. ASQ-3 is scored by assigning points to the responses provided for each question. These points are then totaled to generate a score for each developmental domain. The scoring system typically involves comparing the child's total score to established cutoff points or norms for their age group. Based on this comparison, the child's developmental progress can be categorized as “typical development,” “possible delay

warranting further evaluation," or "significant delay" indicating the need for intervention or support.

2.3 | Statistical Analysis

The distribution of continuous group data was initially assessed using the Shapiro–Wilk test. In cases of missing responses, calculations were made based on the number of participants who provided answers. For categorical variables, data were summarized using frequencies. Continuous variables were summarized using either means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on their distribution. Statistical significance was determined using a significance level of 0.05 ($p < 0.05$). All statistical analyses were performed using SPSS version 29.0 software (IBM Corp.)

3 | Results

3.1 | Baseline Characteristics

Forty-one fetuses were operated at the Ontario Fetal Center during the study period. Short-term outcomes for a subset of this cohort have been previously published [15]. The mean maternal age at the time of surgery was 31.0 ± 5.6 years, and the median GA at surgery was 25.0 weeks (IQR = 1.0). The fetuses were born at a median of 35.9 weeks (IQR = 3.3). Male fetuses constituted a slight majority within the cohort (51.2%). The observed lesion types were either myelomeningocele (62.5%) or myeloschisis (37.5%), with L5 being the most frequent upper lesion level (33.3%). Postnatal weight and height percentages showed a normal distribution, with 25.0% of patients falling between the 50th and 75th percentiles for weight, and 30.0% of patients falling between the 10th and 25th percentiles for height. Not surprisingly, the head circumference of a majority of patients (87.5%) measured at or above the 95th percentile.

Three infants (7.3%) died before the age of one, as previously published [9]. Of the remaining 38 infants, 14 (34.1%) were lost to follow-up despite a multi-pronged attempt at data collection, and medium-term outcomes were available for 24 (58.5%). Baseline characteristics were similar in the study cohort and those lost to follow-up (Supporting Information S1: Appendice 1). The median age at the time of last follow-up was 46.5 months (range 13–74 months).

3.2 | Neurological Outcomes

Sixteen patients (66.7%) did not require CSF diversion procedures. Of the 8 (33.3%) that had undergone procedures, three underwent ventriculoperitoneal (VP) shunting, three endoscopic third ventriculostomy (ETV) and choroid plexus cauterization (CPC), and two underwent a combination of both. One patient required a VP-shunt revision at 17 months of age for shunt malfunction. One patient underwent additional spinal cord untethering surgery (4.2%). No patient experienced seizures or exhibited parent-reported signs of hearing impairment. Only one patient had a suspected mild visual impairment, and three patients (12.5%) required speech therapy.

3.3 | Feeding, Urinary and Bowel Function

Ten children (43.5%) utilized clean intermittent catheterization (CIC) as their bladder management method, followed by spontaneous voiding (34.8%, $n = 8$), or a combination of the two (21.7%, $n = 5$). In the subset of children aged 30 months and older, a slightly higher percentage used only CIC (60.0%, $n = 9$) compared to those who used spontaneous voiding (20.0%, $n = 3$) or a combination of both methods (20.0%, $n = 3$). Ten children (43.5%) required medication for overactive bladder. Among them, 50.0% used an antimuscarinic, 20.0% used an antimuscarinic combined with a prophylactic antibiotic, 20.0% used a beta-3 adrenergic agonist, and 10.0% did not specify the type of medication. Three children (12.5%) received Botox injections for bladder treatment at a median age of 45 months (range: 28–42 months). Regarding gastrointestinal function, all children consumed solid foods by mouth. Eleven children (45.8%) required oral laxatives, three (12.5%) needed a rectal enema daily, and four (16.7%) used a combination of both for constipation. None of the children underwent bowel surgery.

3.4 | Mobility and Ambulation

All patients demonstrated the ability to sit independently, with a large majority (87.5%, $n = 21$) also capable of pulling up to furniture. Fifty percent of the patients ($n = 12$) demonstrated independent walking capabilities outside their residences, while the remaining half ($n = 12$) were able to independently crawl within their homes. It is recognized that patients with open spina bifida tend to exhibit delayed progression in walking skills, with an average estimated delay of 2 years [16]. Slightly better outcomes in walking proficiency were observed among patients aged 30 months and older, with 68.8% ($n = 11$) demonstrating independent walking outside the house, and the remaining 31.3% ($n = 5$) being able to independently crawl indoors. Most patients utilized some form of ambulation aid ($n = 14$, 58.3%), with wheelchairs being the preferred method ($n = 7$, 50.0%), followed by standing frames ($n = 3$, 21.4%), walkers ($n = 2$, 14.2%), or other unspecified ambulation aids ($n = 2$, 14.2%). Among patients capable of independent walking outdoors ($n = 12$, 50.0%), 25.0% ($n = 3$) were able to do so without orthotics or ambulation aid, and 7 (58.3%) were able to do so with orthotics. Two patients required a wheelchair or a walker as an additional walking aid besides their orthotics (16.7%).

Thirteen patients (54.2%) had foot deformities requiring treatment. The majority of these cases (61.5%) were managed conservatively, involving casting or bracing and physiotherapy. Fifteen patients used ankle-foot orthoses (62.5%), one patient a knee-ankle foot brace (4.2%), and two patients a knee-hip-ankle-foot brace (8.3%). Four patients (16.7%) underwent orthopedic surgery. Most patients received physiotherapy, on average twice a month (83.3%) and occupational therapy once a month (54.2%).

3.5 | Developmental Outcomes

Bayley-III scores at 2 years of age were available for 7 children (29.2%). Our cohort showed average scores in language (mean 86.4, SD 10.8) and cognition (mean 87.1, SD 11.9). However, motor function was below average (mean 70.0, SD 9.0). Ages and Stages questionnaires were available for all 24 children in the cohort (Table 1). A majority (79.2%) of children demonstrated "Typical Development" on communication and problem-solving skills. Gross motor development scored notably lower, with 91.7% categorized as "Significantly Delayed" and only 4.2% as "Typical Development." Fine motor skills varied, with 56.5% demonstrating "Typical Development" and 34.8% "Possibly Delayed." Personal-social skills were generally strong, with 70.8% "Typical Development," though 8.3% were "Possibly Delayed."

4 | Discussion

In this study, we present the medium-term outcomes of a cohort who underwent open fetal spina bifida closure. Our findings indicate that while the cohort demonstrated typical developmental scores in communication, problem-solving, and personal-social skills, gross motor skills were significantly delayed. In terms of neurological outcomes, a third of the patients required cerebrospinal fluid diversion procedures. For mobility and ambulation, half of the children were able to walk independently, often with the aid of orthotics or other ambulation supports.

Our study's findings align closely with those from the MOMS trial and the Zurich cohort, particularly in terms of outcomes at 24 and 30 months, motor function, and shunting [5, 6]. In the MOMS trial, fetal surgery was established as a standard of care, demonstrating significant benefits: at 30 months, 42% of children could walk independently, and 40% required VP shunt placement [5]. Similarly, in our study, half of the children could walk independently, often with orthotic support: 25% managed without any aids, and 58.3% with orthotics. Moreover, only 33.3% required CSF diversion procedures [5]. The Zurich cohort, which adhered to the MOMS protocol, reported comparable but slightly varied outcomes [6]. At 24 months, 14% of Zurich patients could walk independently and 55% required shunt placement. These variations may reflect differences in neurosurgical practices and criteria for shunting as well as the timing and tools of developmental assessments (Bayley III in Zurich and our study vs. Bayley II in MOMS). Additional factors such as patient selection criteria, surgical expertise, and postoperative management, including the decision-making process for shunt placement, and the level of multidisciplinary follow-up and support services available to patients and families might also contribute to these discrepancies. Furthermore, our study observed a higher CIC rate at 30 months compared with the MOMS trial [5]. This can be attributed to our proactive approach of initiating CIC at birth, which may explain why our reported CIC rate appears higher than in other centers that may not adopt the same early intervention strategy.

The use of self-reported measures and caregiver assessments, such as the ASQ-3, may introduce subjectivity and recall bias, potentially affecting the accuracy and reliability of our results. Studies comparing the ASQ-3 with standardized tests such as the Bayley-III scale have demonstrated varied results in terms of sensitivity and specificity. For instance, one study found that while the ASQ-3 exhibited high specificity (89.4% among children under 42 months and 92.1% among older children), its sensitivity, particularly for detecting mild delays, was significantly lower than that of other instruments like the SWYC Milestones and PEDS [17]. Another study focusing on preterm and very-low-birthweight infants indicated that the ASQ-3 had a high negative predictive value, especially in the motor domain [18]. However, the ASQ-3's concurrent validity with the Bayley-III scale, particularly in the cognitive domain, was found to be poor, highlighting its limitations in accurately detecting cognitive delays and predicting outcomes at school age [19]. These findings underscore the need for cautious interpretation of ASQ-3 results, acknowledging its strengths in specific domains and its limitations in comprehensive developmental assessment.

The partly retrospective nature of this study design introduces inherent limitations, including reliance on medical records for data extraction, a relatively small sample size, and a single-center setting, which may restrict the generalizability of our findings. Additionally, the absence of a control group hinders our ability to establish causal relationships. The 1-year follow-up period may not capture longer-term outcomes, highlighting the need for further longitudinal studies to assess the persistence of observed effects.

Another limitation is the challenge of obtaining outcomes for patients who deliver at other facilities or whose children do not receive follow-up care at our center. This challenge is not

TABLE 1 | Ages and stages questionnaire subscores.

	Typical development (*N*)	Possible delay (*N*)	Significant delay (*N*)	Incomplete (*N*)	Median score	Minimum score	Maximum score
Communication skills	19	4	1	—	60	20	60
Gross motor skills	1	1	22	—	20	0	60
Fine motor skills	13	8	2	1	40	10	60
Problem solving skills	19	3	2	—	52.5	20	60
Personal-social skills	17	5	2	—	42.5	20	60

unique to our study and has been highlighted by Vergote et al. [20]. Despite patient engagement efforts, including frequent contact with their respective fetal surgeons, our cohort did not show improved participation compared with previous studies. The multidisciplinary nature of care for spina bifida patients complicates data collection across different centers. However, Vergote et al. also found that parents' responses align well with those of the referring centers, indicating that self-reported outcomes can be reliable [20]. Therefore, follow-up through an easily accessible, privacy-safe, hospital-issued online platform, such as a mobile app, could potentially increase patient participation and reduce the rate of lost follow-up data.

Furthermore, while our study focused on outcomes beyond the first year following open fetal spina bifida repair, we acknowledge the broader impact of spina bifida on mental and social well-being throughout an individual's life, extending into adulthood [21, 22]. In addition to evaluating neurological, orthopedic, urological, and gastrointestinal outcomes, it is essential to consider the impact of spina bifida on overall quality of life. Factors such as cognitive function, emotional well-being, social integration, and participation in daily activities are important determinants of quality of life for individuals with spina bifida [23]. Thus, it is crucial to prioritize the creation of a core outcome set for assessing the management and outcomes of individuals who have undergone fetal spina bifida repair to ensure a comprehensive evaluation of these patients.

A core outcome set would standardize the measurement of key variables across studies, ensuring consistency and comparability of findings. By establishing consensus on the most relevant outcomes to measure, such as neurological, orthopedic, urological, gastrointestinal, cognitive, and psychosocial outcomes, researchers can better capture the holistic impact of fetal spina bifida repair and facilitate meaningful comparisons between treatment approaches.

5 | Conclusion

In conclusion, this study highlights the mixed developmental outcomes following open fetal spina bifida repair. While most patients showed normal communication and personal-social skills, gross motor delays were common, and fine motor skills varied. For mobility, half of the children were able to walk independently, often with the aid of orthotics or other supports. Implementing standardized outcome measures and utilizing an accessible platform for patient-reported outcomes could potentially be valuable for improving the quality of follow-up data.

Acknowledgments

The authors have nothing to report.

Ethics Statement

This study was approved by the REBs at Mount Sinai Hospital, The Hospital for Sick Children and Holland Bloorview through Clinical Trials Ontario (CTO Project ID 1660).

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper. The authors have no financial, personal, or professional affiliations that could be perceived as influencing the research presented in this manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.