Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2020;47:91–97
DOI: 10.1159/000500049

Received: January 13, 2019
Accepted after revision: April 1, 2019
Published online: June 5, 2019

Benchmarking against the MOMS Trial: Zurich Results of Open Fetal Surgery for Spina Bifida

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Keywords

Benchmark comparison · Spina bifida · Neural tube defect · Myelomeningocele · Myeloschisis · Fetus · Fetal surgery · Fetal repair · In utero surgery

Abstract

Introduction: The Management of Myelomeningocele Study, a.k.a. the MOMS trial, was published in 2011 in the *New England Journal of Medicine*. This prospective randomized controlled trial proved to be a milestone publication that provided definitive evidence that fetal surgery is a novel standard of care for select fetuses with spina bifida aperta (SB). The goal of our study is to assess whether our center can match these benchmark results. ***Materials and Methods:*** Our study was conducted according to the MOMS protocol using the same inclusion and exclusion criteria and looked at the same outcome parameters that were used in the MOMS trial. Zurich and MOMS results were compared. ***Results:*** We enrolled 20 patients between December 2010 and

Ueli Möhrlen and Nicole Ochsenbein-Kölble share first authorship, and Roland Zimmermann and Martin Meuli share last authorship. Presented as an oral presentation at the 37th Annual Meeting of the International Fetal Medicine and Surgery Society, August 7–12, 2018, Bali, Indonesia.

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May 2015 all of whom underwent fetal surgery for SB. Among 51 different outcome variables, there were only 3 favorable (multiplicity-adjusted) significant differences (gestational age at birth, hindbrain herniation, and psychomotor development). There were no statistically significant differences regarding any other parameters. ***Conclusion:*** Our findings confirm that rigorous apprenticeship, training, and comprehensive prospective data collection enable centers like the Zurich Center for Fetal Diagnosis and Therapy to achieve benchmark results for open fetal surgery for myelomeningocele and myeloschisis. These results justify the existence and continuation of our program. Outcome documentation is an essential element of quality management. It is medically and ethically fundamental for fetal medicine and surgery centers offering high-end innovative medical care.

Introduction

Experimental evidence from the fetal sheep model [1–3] and from analyses of aborted human fetuses [4, 5] paved the way to open human fetal surgery for myelomeningocele (MMC; for simplicity, the abbreviation MMC stands for both myelomeningocele and its noncystic variant, called myeloschisis) [6, 7]. Based on encouraging results, a large prospective, randomized, human fetal surgery clinical trial was carried out between 2003 and 2010 in 3 US clinical centers, the Management of Myelomeningocele Study (MOMS) [8]. The goal was to compare fetal versus postnatal surgery. The trial was stopped prematurely for better results in the fetal surgery group. The key findings of this milestone article, published in 2011 by *The New England Journal of Medicine*, were that fetal surgery, although not curative, and although associated with maternal and fetal risks, represents a valid option of care. The primary benefits were a higher rate of reversal of hindbrain herniation, a significantly lower rate of shunting for hydrocephalus, and a significantly better rate of independent ambulation.

As a consequence of this breakthrough, the Zurich Center for Fetal Diagnosis and Therapy opened its own fetal surgery program in December 2010. As of this date, over 100 open fetal surgeries for MMC have been successfully performed.

The MOMS results still represent the current benchmark. The goal of our study, therefore, was to investigate whether our program can replicate these reference results, as this would be vital quality information for both our center and our patients.

Materials and Methods

At the very beginning of our program, a data registry was created to record all pertinent data in a prospective and comprehensive way. Of note, this registry includes, but is not limited to, the same demographic and 51 outcome variables as examined in the MOMS trial (the plan to carry out a comparative study to the MOMS trial was already established at the time of the center's conception). All data for the present study were retrieved from this repository. The study was approved by our local Ethics Committee (KEK-ZH No. 2015-0172), and parents gave written informed consent.

Multidisciplinary diagnostic workup, application of inclusion and exclusion criteria, nondirective prenatal counselling, obtaining written informed consent, perioperative management, as well as the maternal-fetal general anesthesia and surgery were basically done in accordance with the protocols and surgical techniques used during the MOMS trial.

All patients, irrespective of their country of origin, were scheduled to be re-hospitalized in our center at 34 weeks of gestation for expectant management and antepartum monitoring with the plan for elective caesarean section at 37 weeks.

After birth, babies were transferred to the multidisciplinary Pediatric Spina Bifida Center (which is an integral part of the University Children's Hospital Zurich) for standard baseline postnatal diagnostic workup, setting up a patient (and family)-specific therapeutic regimen, detailed instruction of parents, and preparation for a smooth transition to home after discharge. Subsequently, all patients were scheduled for routine follow-up appointments at our interdisciplinary Pediatric Spina Bifida Center at 3, 6, 9, 12, 18, and 24 months after discharge (including but not limited to clinical examination by a multidisciplinary expert team, MRI, bladder and rectum manometry). Thereafter, follow-up appointments continue at yearly intervals up to 18 years of age. Developmental assessment was performed with the Bayley Scales of Infant and Toddler Development (Bayley III) [9].

For the purpose of this study, we were using the same result tables (structure and parameters/variables) as the ones published in the aforementioned *New England Journal of Medicine* article and entered our data to allow for direct numerical and statistical comparison. Our center's first 20 patients undergoing fetal surgery for spina bifida aperta were enrolled from December 2010 to May 2015 with a minimal follow-up of 24 months. End points to be compared were collected from follow-up appointments at 12 and 24 months. The prospectively collected dataset was complete with no loss of follow-up. Statistical analyses were done using SPSS version 23 for Windows. Differences in proportions were compared using the χ^2 test, and the significance level was set at $p \leq 0.05$. If the counts were too low (predicted in the χ^2 test <5), the Fisher exact test was used instead of the χ^2 test. In case of multiple tests, Bonferroni adjustment was performed. The between-group comparison was performed with the use of the Cochran-Armitage test for trend.

Results

From December 2010 through May 2015, 20 patients underwent fetal surgery for MMC repair. All infants were delivered by cesarean section in our center and included in the study. There was no maternal mortality. One pa-

Table 1. Population characteristics

Characteristics	MOMS (n = 78)	Zurich (n = 20)	p
Fetal sex female, n (%)	35 (45)	10 (50)	0.68
Maternal age at screening, years	29.3±5.3	30.4±4.8	0.40
Race or ethnic group, n (%)			0.28
White	73 (94)	17 (85)	
Black	1 (1)	1 (5)	
Hispanic	2 (3)	1 (5)	
Other	2 (3)	1 (5)	
Married or living with partner, n (%)	73 (94)	19 (95)	0.81
Years of schooling	14.8±1.7	N/A	
Body mass index	26.2±3.7	26.2±4.1	1.0
Current smoker, n (%)	6 (8)	0 (0)	0.34
Either parent with familial history of neural tube defect, n (%)	8 (10)	0 (0)	0.20
Nullipara, n (%)	33 (42)	10 (50)	0.54
Previous uterine surgery, n (%)	11 (14)	2 (10)	1.00
Cervical length, mm	38.9±7.3	42.1±5.1	0.07
Anterior placenta, n (%)	36 (46)	11 (55)	0.48
Lesion level on ultrasonography, n (%)			0.49
Thoracic	4 (5)	0 (0)	
L1–L2	21 (27)	3 (15)	
L3–L4	30 (38)	11 (55)	
L5–S1	23 (29)	6 (30)	
Lesion level L3 or lower on ultrasonography, n (%)	53 (68)	17 (85)	0.13
Club foot on ultrasonography, n (%)	20 (26)	2 (10)	0.23

Values are means ± SD, unless otherwise indicated.

tient died on the first day of life (5%) due to unexplained severe lung hypoplasia and intractable respiratory failure.

All of the remaining 19 patients were examined according to exactly the same parameters as used in the MOMS trial. The only deviation was that 15 of the 19 surviving patients (4 were too young to be examined) underwent neurodevelopmental assessment at 24 months instead of at 30 months (see Discussion section). For all parameters, the Zurich data were compared with the MOMS data and statistically analyzed. All results are shown in Tables 1–4. The most relevant findings are commented on below in the Discussion section.

Discussion

This is the first study from a non-MOMS center to replicate the open fetal surgery arm of the MOMS trial to prove that benchmark results can be obtained outside the rigors of a clinical trial such as MOMS. When the MOMS trial was published, an editorial comment expressed skepticism as to whether non-MOMS trial centers could deliver MOMS quality results [10]. We demonstrate that the Zurich Center for Fetal Diagnosis and Therapy has generated results that are at least equivalent to MOMS.

For the sake of transparency, the following points hinder a "perfect" comparison: first, we compare 78 MOMS fetal surgery patients, treated between 2003 and 2010, with our first 20 fetal surgery patients, treated between 2010 and 2015. Then, we disclose the partnership with the Department of Surgery of the Children's Hospital of Philadelphia (CHOP) and that 1 member of the CHOP fetal surgeons assisted in the treatment of our first 11 cases. Finally, developmental testing was performed at 24 months with the newest Bayley version instead of at 30 months as in the MOMS trial.

In the vast majority of variables, there was no statistically significant difference between our results and MOMS. Importantly, there were no significant differences regarding all 20 population characteristics (Table 1).

For certain variables, we had unfavorable results compared with the MOMS trial (Tables 2–4). Regarding maternal outcomes, we noted a higher rate of spontaneous labor (65 vs. 38%, p = 0.03). In terms of postneonatal outcome, the only difference was a high incidence of epidermoid cysts (28 vs. 3%, p = 0.004). Three out of 5 cases

Table 2. Maternal outcome and fetal or neonatal outcome

	MOMS (n = 78)	Zurich (n = 20)	p	Bonferroni-adjusted p value
Maternal outcome				
Chorioamniotic membrane separation, n (%)	20 (26)	5 (25)	0.95	1.00
Pulmonary edema, n (%)	5 (6)	0 (0)	0.58	1.00
Oligohydramnios, n (%)	16 (21)	4 (20)	1.00	1.00
Placental abruption, n (%)	5 (6)	0 (0)	0.58	1.00
Gestational diabetes, n (%)	4 (5)	3 (15)	0.15	1.00
Chorioamnionitis, n (%)	2 (3)	0 (0)	1.00	1.00
Preeclampsia or gestational hypertension, n (%)	3 (4)	0 (0)	1.00	1.00
Spontaneous membrane rupture, n (%)	36 (46)	7 (35)	0.37	1.00
Spontaneous labor, n (%)	30 (38)	13 (65)	0.03	1.00
Blood transfusion at delivery, n (%)	7 (9)	0 (0)	0.34	1.00
Status of hysterotomy site at delivery, n/total n (%)			0.20[a]	1.00
Intact, well-healed	49/76 (64)	8/20 (40)		
Very thin	19/76 (25)	10/20 (50)		
Area of dehiscence	7/76 (9)	2/20 (10)		
Complete dehiscence	1/76 (1)	0/20 (0)		
Fetal or neonatal outcome				
Bradycardia during fetal repair, n (%)	8 (10)	1 (5)	0.68	1.00
Perinatal death, n (%)	2 (3)	1 (5)	0.50	1.00
Gestational age at birth, weeks	34.1±3.1	35.6±9.2	<0.0001	<0.0001
Gestational age at birth, n (%)			0.04[a]	1.00
<30 weeks	10 (13)	0 (0)		
30–34 weeks	26 (33)	5 (25)		
35–36 weeks	26 (33)	8 (40)		
≥37 weeks	16 (21)	7 (35)		
Birth weight				
Mean, g	2,383±688	2,742±393	0.03	1.00
Less than 3rd percentile, n (%)	0	1 (5)	0.20	1.00
Less than 10th percentile, n (%)	3 (4)	2 (10)	0.27	1.00
Dehiscence at repair site, n/total n (%)	10/77 (13)	1/20 (5)	0.45	1.00
Apnea, n/total n (%)	28/77 (36)	1/20 (5)	0.006	0.31
Pneumothorax, n/total n (%)	1/77 (1)	1/20 (5)	0.37	1.00
Respiratory distress syndrome, n/total n (%)	16/77 (21)	7/20 (35)	0.24	1.00
Patent ductus arteriosus, n/total n (%)	3/77 (4)	0/20 (0)	1.00	1.00
Sepsis, n/total n (%)	4/77 (5)	1/19 (5)	1.00	1.00
Necrotizing enterocolitis, n/total n (%)	1/77 (1)	0/19 (0)	1.00	1.00
Periventricular leukomalacia, n/total n (%)	4/77 (5)	0/20 (0)	0.58	1.00
Foot deformity, n/total n (%)	39/78 (50)	5/20 (25)	0.045	1.00

Values are means ± SD, unless otherwise indicated. [a] The between-group comparison was performed with the use of the Cochran-Armitage test for trend.

underwent resection because of growth and/or symptoms, while 2 are being closely monitored.

In the following domains, our results compare favorably with MOMS (Tables 2–4). Concerning neonatal outcomes, the gestational age at birth was significantly higher in the Zurich group than in MOMS (35.6 vs. 34.1 weeks, p < 0.0001) with consequently higher birth weights (2,742 vs. 2,383 g, p = 0.03) and lower rates of apnea (5 vs. 36%, p = 0.006). We assume that these favorable findings result from using atosiban (Tractocile, Ferring AG, Baar, Switzerland), an extremely potent tocolytic not available in the USA [11].

Also, the Zurich patients demonstrate better results regarding cerebrospinal pathologies (Table 3). Complete hindbrain reversibility was found in 94% of our patients

Table 3. Infant outcome at 12 months

	MOMS (n = 78)	Zurich (n = 20)	p	Bonferroni-adjusted p value
Primary outcome, n (%)	53 (68)	12 (60)	0.50	1.00
Components of the primary outcome, n (%)			0.06	1.00
Death before shunt placement	2 (3)	1 (5)		
Shunt criteria met	51 (65)	11 (55)		
Shunt placed without meeting criteria	0	0		
Placement of shunt, n (%)	31 (40)	11 (100)	0.15	1.00
Any hindbrain herniation, n/total n (%)	45/70 (64)	1/18 (6)	<0.0001	0.0005
Degree of hindbrain herniation, n/total n (%)			<0.0001	0.005
None	25/70 (36)	17/18 (94)		
Mild	28/70 (40)	1/18 (6)		
Moderate	13/70 (36)	0/18 (0)		
Severe	4/70 (19)	0/18 (0)		
Any brainstem kinking, n/total n (%)	14/70 (20)	1/18 (6)	0.29	1.00
Degree of brainstem kinking, n/total n (%)			0.10[a]	1.00
None	56/70 (80)	17/18 (94)		
Mild	4/70 (6)	1/18 (6)		
Moderate	7/70 (10)	0/18 (0)		
Severe	3/70 (4)	0/18 (0)		
Abnormal location of fourth ventricle, n/total n (%)	32/70 (46)	2/18 (11)	0.01	0.51
Location of fourth ventricle, n/total n (%)			0.01[a]	0.51
Normal	38/70 (54)	16/18 (89)		
Low	28/70 (40)	2/18 (11)		
At foramen magnum	1/70 (1)	0/18 (0)		
Below foramen magnum	3/70 (4)	0/18 (0)		
Syringomyelia, n/total n (%)	27/69 (39)	9/18 (50)	0.40	1.00
Epidermoid cyst, n/total n (%)	2/67 (3)	5/18 (28)	0.004	0.2
Surgery for tethered cord, n/total n (%)	6/77 (8)	0/18 (0)	0.59	1.00
Chiari decompression surgery, n/total n (%)	1/77 (1)	0/18 (0)	1.00	1.00
Shunt infection, n/total n (%)	5/77 (6)	0/18 (0)	0.58	1.00

[a] The between-group comparison was performed with the use of the Cochran-Armitage test for trend.

versus in 36% of MOMS patients ($p < 0.0001$). A discrepancy was found between shunt criteria met (in 55% of our patients vs. in 65% of MOMS patients, p = not significant [ns]) and patients actually shunted (the same 55% of our patients, but only 40% of the 65% of MOMS patients meeting the shunt criteria were shunted, p = ns), suggesting a difference in neurosurgical practice between the MOMS trial centers and Zurich.

Neonatal foot deformities were present in 25% of Zurich and in 50% of MOMS patients ($p = 0.045$) (Table 2). The comparison of the differences between motor function and anatomical levels yielded more favorable results for the Zurich cohort, but none reached statistical significance (Table 4).

Regarding independent walking and walking status, the results of the Zurich group were somewhat worse, but differences were not significant (Table 4). Taken together, there are no significant disparities regarding lower extremity motor function between the 2 cohorts.

The last considerations regard postnatal development (Table 4). In contrast to the MOMS trial, our outcome assessment was performed at 24 months and not at 30 months using the third Bayley version. As results are expressed as standard scores (mean 100, 1 SD 15), no age effect is introduced. However, because of different normative samples, comparing results obtained from Bayley II (MOMS) with those from Bayley III (current study) is limited as scores tend to be higher with the Bayley III version [12]. Despite these methodological aspects, the cognitive outcome of our population is comparable to MOMS.

Table 4. Outcomes of children at 30 months (MOMS) and at 24 months (Zurich cohort)

	At 30 months, MOMS (n = 64)	At 24 months, Zurich (n = 15)	p	Bonferroni-adjusted p value
Primary outcome score	149±57.5	N/A (N/A)	0.02	1.00
Primary outcome components				
Mental Development Index Bayley II	89.7±14	80.3±13.1[a]		
Cognitive Composite Score Bayley III	N/A (N/A)	92.9±10.3		
Difference between motor function and anatomical levels	0.58±1.94	1.1±1.5	0.33	1.00
Mental Development Index Bayley II, *n*/total *n* (%)				
≥50	60/62 (97)	15/15 (100)	1.00	1.00
≥85	46/62 (74)	6/15 (40)	0.02	1.00
Difference between motor function and anatomical levels, *n*/total *n* (%)			0.12[b]	1.00
≥Two levels better	20/62 (32)	5/14 (36)		
One level better	7/62 (11)	4/14 (29)		
No difference	14/62 (23)	4/14 (29)		
One level worse	13/62 (21)	1/14 (7)		
≥Two levels worse	8/62 (13)	0/14 (0)		
Psychomotor Development Index Bayley II				
Mean ± SD	64±17.4	65.7±7.7[a]	0.71	1.00
≥50, *n*/total *n* (%)	29/62 (47)	13/13 (100)	<0.0001	0.02
≥85, *n*/total *n* (%)	10/62 (13)	1/13 (8)	0.68	1.00
Motor Composite Score Bayley III				
Mean ± SD	N/A (N/A)	75.6±5.3		
≥50, *n*/total *n* (%)	N/A (N/A)	12/12 (100)		
≥85, *n*/total *n* (%)	N/A (N/A)	1/12 (8)		
Peabody Development Motor Scale				
Stationary score	7.4±1.1	N/A (N/A)		
Locomotion score	3±1.8	N/A (N/A)		
Object manipulation score	5.1±2.6	N/A (N/A)		
Walking independently on examination, *n*/total *n* (%)	26/62 (42)	2/14 (14)	0.053	1.00
Walking status, *n*/total *n* (%)			0.45[b]	1.00
None	28/62 (29)	5/14 (36)		
Walking with orthotics or devices	18/62 (29)	7/14 (50)		
Walking without orthotics	26/62 (42)	2/14 (14)		
WeeFIM score				
Self-care	20.5±4.2	N/A (N/A)		
Mobility	19.9±6.4	N/A (N/A)		
Cognitive	23.9±5.2	N/A (N/A)		

Values are means ± SD, unless otherwise indicated. [a] Calculated based on the suggested transformation by Jary et al. [14]. [b] The between-group comparison was performed with the use of the Cochran-Armitage test for trend.

Of note, all comparisons are based on the statistical results generated by the Fisher exact tests and the χ^2 tests comparing single variables. Since we analyzed multiple outcome variables (n = 51), it was imperative to calculate a Bonferroni adjustment for multiplicity, leading to a substantial reduction of significant differences. The 3 favorable significant differences remaining are a higher gestational age at birth, less hindbrain herniation, and 1 better parameter regarding psychomotor development (Tables 2–4).

Finally, Moldenhauer et al. [13] have recently published the CHOP post-MOMS experience. They found that results were comparable to MOMS. When comparing our results with Moldenhauer et al.'s, we find that they are comparable as well (Table 5).

The above quoted post-MOMS article [13] also fuels a broader view: now, almost a decade after the completion of MOMS, it is time to gradually move beyond MOMS as a gold standard. This plea for new horizons embraces a fresh look at inclusion and exclusion criteria, testing novel techniques, and also defining new standards based on proper results. In fact, we are addressing such issues in current studies enrolling more than 100 patients operated so far (December 2018).

Table 5. Comparison of key findings of single-center post-MOMS [13] data with Zurich Center data

	CHOP [13] (n = 100)	Zurich (n = 20)
Membrane separation, %	22.9	25.0
Preterm premature rupture of membranes, %	32.3	35.0
Preterm labor, %	37.5	65.0
Average gestational age at delivery, weeks	34.3	35.6
Rate of perinatal loss, %	6.1	5.0
Woman received transfusions, %	3.4	0.0
Neonates with no evidence of hindbrain herniation on MRI, %	71.1	94.0
Children with a functional level of ≥1 better than the prenatal anatomical level, %	55.0	60.0

In conclusion, the Zurich Center for Fetal Diagnosis and Therapy has generated benchmark results regarding open fetal surgery for MMC. This finding justifies the existence and, in particular, continuation of our program. More generally, these results confirm that with rigorous apprenticeship, training, and fastidious attention to detailed, well-delineated, and prospective data collection on every case it is possible for centers like the Zurich Center for Fetal Diagnosis and Therapy to deliver benchmark results for open fetal surgery for MMC. Finally, comprehensive outcome documentation is medically and ethically imperative. It is an instrumental element of quality management for fetal medicine and surgery centers offering high-end innovative medical care.

Acknowledgments

We express our gratitude to the Claus Cramer-Stiftung and to Mr. Stefan Schauer for their generous support.

Statement of Ethics

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflict of interest du declare.

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