HHS Public Access

Author manuscript

J Neurosurg Pediatr. Author manuscript; available in PMC 2017 January 03.

Published in final edited form as:

J Neurosurg Pediatr. 2015 December ; 16(6): 613–620. doi:10.3171/2015.7.PEDS15336.

Prenatal surgery for myelomeningocele and the need for cerebrospinal fluid shunt placement

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Abstract

Object—The Management of Myelomeningocele Study (MOMS) was a multicenter randomized trial comparing the safety and efficacy of prenatal and postnatal closure of myelomeningocele. The trial was stopped early because of the demonstrated efficacy of prenatal surgery, and outcomes on 158 of 183 pregnancies were reported. Here, the authors update the 1-year outcomes for the complete trial, analyze the primary and related outcomes, and evaluate whether specific prerandomization risk factors are associated with prenatal surgery benefit.

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Clinical trial registration no.: NCT 00060606 (clinicaltrials.gov)

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Supplemental Information

Previous Presentation

Portions of this paper were presented at the American Association of Neurological Surgeons/Congress of Neurological Surgeons Pediatric Section Annual Meeting, Jacksonville, Florida, December 5, 2014.

Author Contributions

Conception and design: Tulipan, Thom, Burrows, Walsh, Wellons. Acquisition of data: Tulipan, Thom, Gupta, Sutton, Burrows, Farmer, Walsh, Johnson, Adzick. Analysis and interpretation of data: Tulipan, Thom, Burrows, Adzick, Wellons. Drafting the article: Tulipan, Thom, Burrows, Adzick, Wellons. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Thom, Burrows. Administrative/technical/material support: Tolivaisa.

Methods—The primary outcome was a composite of fetal loss or any of the following: infant death, CSF shunt placement, or meeting the prespecified criteria for shunt placement. Primary outcome, actual shunt placement, and shunt revision rates for prenatal versus postnatal repair were compared. The shunt criteria were reassessed to determine which were most concordant with practice, and a new composite outcome was created from the primary outcome by replacing the original criteria for CSF shunt placement with the revised criteria. The authors used logistic regression to estimate whether there were interactions between the type of surgery and known prenatal risk factors (lesion level, gestational age, degree of hindbrain herniation, and ventricle size) for shunt placement, and to determine which factors were associated with shunting among those infants who underwent prenatal surgery.

Results—Ninety-one women were randomized to prenatal surgery and 92 to postnatal repair. The primary outcome occurred in 73% of infants in the prenatal surgery group and in 98% in the postnatal group ($p < 0.0001$). Actual rates of shunt placement were only 44% and 84% in the 2 groups, respectively ($p < 0.0001$). The authors revised the most commonly met criterion to require overt clinical signs of increased intracranial pressure, defined as split sutures, bulging fontanelle, or sunsetting eyes, in addition to increasing head circumference or hydrocephalus. Using these modified criteria, only 3 patients in each group met criteria but did not receive a shunt. For the revised composite outcome, there was a difference between the prenatal and postnatal surgery groups: 49.5% versus 87.0% ($p < 0.0001$). There was also a significant reduction in the number of children who had a shunt placed and then required a revision by 1 year of age in the prenatal group (15.4% vs 40.2%, relative risk 0.38 [95% CI 0.22–0.66]). In the prenatal surgery group, 20% of those with ventricle size < 10 mm at initial screening, 45.2% with ventricle size of 10 up to 15 mm, and 79.0% with ventricle size ≥ 15 mm received a shunt, whereas in the postnatal group, 79.4%, 86.0%, and 87.5%, respectively, received a shunt ($p = 0.02$). Lesion level and degree of hindbrain herniation appeared to have no effect on the eventual need for shunting ($p = 0.19$ and $p = 0.13$, respectively). Similar results were obtained for the revised outcome.

Conclusions—Larger ventricles at initial screening are associated with an increased need for shunting among those undergoing fetal surgery for myelomeningocele. During prenatal counseling, care should be exercised in recommending prenatal surgery when the ventricles are 15 mm or larger because prenatal surgery does not appear to improve outcome in this group. The revised criteria may be useful as guidelines for treating hydrocephalus in this group.

Keywords

myelomeningocele; spina bifida; hydrocephalus; hindbrain herniation; fetal surgery; cerebrospinal fluid shunt; congenital

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The Management of Myelomeningocele Study (MOMS) was a randomized controlled trial to compare the safety and efficacy of prenatal repair of myelomeningocele with that of standard postnatal repair. Recruitment to the trial was halted in 2010 according to predefined stopping rules after 183 (92%) of the planned sample size of 200 women had been randomized. The trial was stopped early because of the demonstrated efficacy of prenatal surgery, and outcomes on 158 of 183 pregnancies were reported. In summary, prenatal surgery was associated with less need for a CSF shunt in children at 12 months and a better composite score for mental development and motor function at 30 months.[1] Prenatal surgery

also showed benefit in several key secondary outcomes, including hindbrain herniation and the ability to walk unaided.[1] These results were tempered by an increase in preterm birth and the occurrence of uterine dehiscence in the prenatal surgery group. The initial published results included only data that were available at the time as recommended by the Data and Safety Monitoring Committee to ensure swift publication. This report presents the final outcome data up to 12 months of age.

The first primary outcome was a composite of death or the need for a CSF shunt in the children by 12 months of age. Before the trial began, we specified objective criteria for shunt placement because of the concern that there could be bias. Not only do pediatric neurosurgeons have different criteria for surgical intervention for hydrocephalus, these criteria can at times be subjective and variable depending on the individual case. Of even more concern was the potential for differential criteria to be used for children in the prenatal versus postnatal surgery groups. It was anticipated that there might be a lower threshold for shunt placement in children who had undergone postnatal repair. Therefore, children who met the criteria were deemed to have reached the primary end point, regardless of whether a shunt was placed. It was evident from the results, however, that during the 8 years of recruitment, the management of hydrocephalus had evolved. In the published cohort, about one-quarter of the children in the prenatal surgery group and 10% in the postnatal surgery group met the criteria but did not have a shunt placed. This warranted a more in-depth investigation as to which specific criteria did not result in shunt placement and the proportion of children meeting criteria between the two groups.

One of the other important issues that has yet to be addressed is whether the criteria used in practice today to screen patients for prenatal surgery can be refined such that those fetuses that are most likely to benefit from the surgery as children can be identified, and those women whose fetuses are unlikely to benefit from surgery can be spared the potential risks of intrauterine repair, which include preterm delivery and uterine dehiscence. If this could be accomplished, our ability to counsel pregnant women would be substantially improved, thus simplifying what is currently still a difficult decision-making process for prospective parents and treating physicians alike.

Methods

The MOMS was conducted by Children's Hospital of Philadelphia, Vanderbilt University, and the University of California, San Francisco, each an established maternalfetal surgery center, and by an independent data coordinating center (George Washington University Biostatistics Center) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (clinical trial registration no. NCT 00060606 [clinicaltrials.gov]). Details of the trial design and procedures have been previously published.[1] Briefly, eligible pregnant women with a fetus diagnosed with myelomeningocele between 19 and 25 weeks of gestation were randomized at one of the 3 maternal-fetal surgery centers to either prenatal or postnatal surgical repair. If randomized to prenatal surgery, the participant underwent hysterotomy to repair the fetal myelomeningocele shortly after randomization, and stayed at the center with close monitoring and follow-up until delivery. If a woman was randomized to postnatal surgery, she went home and returned at 37 weeks for delivery and repair of the

myelomeningocele, which was performed within 48 hours of birth. All infants were delivered via cesarean section, which was scheduled at 37 weeks of gestation if not already delivered, and families returned to the maternal-fetal surgery centers for follow-up of the children at 12 and 30 months of age.

The primary outcome was a composite of fetal loss or any of the following: infant death, CSF shunt placement, or meeting the prespecified criteria for shunt placement before 1 year of age. The composite was chosen to avoid the problem of competing risks, which can be a source of bias.[6] The first objective criterion was the occurrence of at least 2 of the following: a) an increase in the greatest occipital- frontal circumference adjusted for gestational age, defined as crossing percentiles (if a plateau was reached, this did not qualify); b) bulging fontanelle (assessed when the baby was in an upright position and not crying) or split sutures or sunsetting sign; c) increasing hydrocephalus on consecutive imaging studies determined by an increase in ratio of biventricular diameter to biparietal diameter according to the method of O'Hayon et al.;[9] or d) head circumference > 95th percentile for gestational age. Criteria 2, 3, and 4 were the presence of marked syringomyelia with ventriculomegaly, ventriculomegaly with symptoms of Chiari malformation (stridor, swallowing difficulties, apnea, bradycardia), and persistent CSF leakage from the myelomeningocele wound or bulging at the repair site, respectively. If a child met any one of the 4 criteria by 12 months of age, he or she was deemed to have met the criteria for shunt treatment, and therefore the primary outcome. For purposes of the current analysis, a secondary outcome was additionally studied, namely the need for shunt revision prior to 1 year of age.

By protocol, the neurosurgeon at the maternal-fetal surgery center contacted the local neurosurgeon to review the criteria before a patient returned home after delivery, to review the study criteria for shunting, and to encourage consultation before shunt placement. Copies of medical records and imaging studies up to 12 months of age for all infants were sent to the coordinating center, which was responsible for ensuring that the medical records did not reveal the assigned surgery group of the infant. Information in the medical records was transcribed, and measure ments were converted to percentiles to mask gestational age at birth. The MRI study obtained at the 12-month visit to the MOMS center was included in the medical records to be reviewed. An independent committee of pediatric neurosurgeons, blinded to the treatment assignment, reviewed the clinical and radiological data for each child to determine whether criteria for shunt placement were met.

A sample size of 100 patients per group yielded over 90% power, with a 2-sided Type I error of 5%, to detect a 28% reduction in the primary outcome, assuming an 80% shunt rate in children receiving postnatal surgery who survived to 1 year,[10] a 30% reduction in the primary outcome among the survivors in the prenatal surgery group, a 5% rate of death before shunt placement, and a 5% loss to follow-up.

In the univariable analysis, categorical variables were compared using the chi-square test. Relative risks and 95% confidence intervals were calculated. Exact methods were used where appropriate. Continuous variables were compared with the Wilcoxon rank-sum test. Analysis was by intent to treat. The prespecified criteria for shunt placement were examined

in detail to determine whether revised criteria could be constructed that would improve the false-positive rate (meeting criteria without shunt placement).

Interaction tests were conducted using logistic regression for ad hoc subgroup analyses of outcome by the 4 prenatal variables of interest determined at prenatal ultrasound screening: ventricular size, lesion level, degree of hindbrain herniation, and estimated gestational age. Multivariable logistic regression was also conducted to evaluate whether any of these risk factors are associated with shunt placement or meeting criteria for a shunt within the prenatal surgery cohort. For the primary outcome, the 96.2% confidence interval is reported, to account for the previous looks at the data, as described in the original report. [1] For secondary outcomes, a nominal p value < 0.05, without adjustment for multiple comparisons, was considered to indicate statistical significance.

Results

Update on the Entire Trial Cohort

A total of 183 women were randomized, 91 in the prenatal surgery group and 92 in the postnatal surgery group (Fig. 1), representing an additional 25 women since the previous report. The baseline characteristics of the entire trial cohort are presented in Table 1. As previously published, there were no differences between the surgery groups except for spina bifida lesion level L-3 or lower (68.1% in the prenatal surgery group and 82.6% in the postnatal surgery group; $p = 0.02$) and sex (46.2% of patients were female in the prenatal surgery group vs 62.0% in the postnatal surgery group; $p = 0.03$).

The primary outcome was present in 66 children (72.5%) in the prenatal surgery group and 90 children (97.8%) in the postnatal surgery group (RR 0.74 [96.2% CI 0.65–0.85], $p < 0.0001$) (Table 2). Actual rates of shunt placement were 44.0% in the prenatal surgery group and 83.7% in the postnatal surgery group (RR 0.53 [95% CI 0.41–0.67], $p < 0.0001$). The results were similar when adjusted by lesion level and sex. There was also a significant difference in the proportion of children who had a shunt placed and then required a revision by 1 year of age (15.4% vs 40.2%, RR 0.38 [95% CI 0.22–0.66], $p < 0.001$).

Evaluation of Shunt Criteria

Four children, all in the postnatal surgery group, had shunts placed without meeting the criteria; however, 37 children did not have shunts placed despite meeting criteria (26.4% in the prenatal surgery group versus 14.1% in the postnatal surgery group, $p = 0.04$). The most commonly met criterion for shunt placement in both groups was Criterion 1, i.e., 2 or more of the following: a) age-adjusted head circumference crossing percentiles; b) bulging fontanelle or split sutures or sunsetting sign; c) increasing hydrocephalus on consecutive imaging; or d) head circumference > 95th percentile. All children who met the primary outcome in the prenatal surgery group and 91% of those in the postnatal group met this criterion. Thirty-five of the 112 children (31.3%) who met Criterion 1 without Criteria 2–4 did not have shunts placed. Of the children who did not meet Criteria 2–4 but met Criterion 1 because they had overt clinical signs of increased intracranial pressure defined as split sutures, bulging fontanelle, or sunsetting eyes, only 2 of 21 (9.5%) in the prenatal surgery

group and 2 of 35 (5.7%) in the postnatal surgery group did not receive a shunt (p = 0.63). Criteria 2 and 3 (presence of syringomyelia and ventriculomegaly with symptomatic Chiari II malformation as manifested by stridor, swallowing difficulty, and so on) were relatively rare, and the overall frequency was not different between the 2 groups. However, leakage at the myelomeningocele site as a criterion for shunt placement (Criterion 4) was significantly different between the 2 groups: 1 (1.1%) in the prenatal surgery group and 23 (25.0%) in the postnatal surgery group (p < 0.0001), and this difference accounted for approximately 60% of the overall difference in shunt placement between the 2 groups.

We then modified the original study criteria such that Criterion 1 required bulging fontanelle or split sutures or sunsetting sign with at least 1 of the other original components of Criterion 1. Under these modified criteria, the proportion of infants in both groups who met criteria without shunt placement was 3% in both groups, and the number of infants who did not meet criteria but did have a shunt placed was 15 (16.5%) in the prenatal surgery group and 14 (15.2%) in the postnatal surgery group (Table 2). Since one-fifth of the children who met criteria did not have a shunt placed, a revised composite was constructed, consisting of fetal death or any of the following: infant death, CSF shunt placement or meeting the revised criteria for shunt placement before 1 year of age. Further analyses were conducted using the revised composite as well as actual shunt placement.

Prenatal Risk Factors for Shunt Placement

Logistic regression analysis adjusting for sex and lesion level, which were imbalanced between the 2 groups, revealed that ventricular size at screening and gestational age at randomization were associated with a differential effect of prenatal surgery on shunt placement and on the revised composite (p values for interaction < 0.05 and < 0.01, respectively; Table 3). In the prenatal surgery group, 20.0% of those with ventricle size < 10 mm, 45.2% with ventricle size of 10 up to 15 mm, and 79.0% with ventricle size ≥ 15 mm received a shunt, whereas in the postnatal group, 79.4%, 86.0%, and 87.5%, respectively, required a shunt (p = 0.01). In the prenatal surgery group, 31.4% of children whose mothers were randomized at ≤ 23 weeks of pregnancy and 60.0% randomized at ≥ 24 weeks underwent shunt treatment compared with 86.1% and 81.6% in the postnatal group. We also found concordant results for the revised outcome.

Multivariable logistic regression for the prenatal surgery group only, which included all 4 prenatal risk factors of interest as well as sex, showed that only ventricle size was significantly associated with shunt placement or the revised composite outcome, with odds ratios of 1.46 (95% CI 1.20–1.79) and 1.57 (95% CI 1.26–1.97), respectively. Gestational age after adjusting for ventricle size was no longer significant (Table 4). Lesion level and degree of hindbrain herniation appeared to have no effect on the eventual need for shunting (p = 0.19 and p = 0.13, respectively).

Discussion

The final results for the infants at 1 year of age whose mothers participated in the MOMS trial are consistent with the previously published results.[1,4] This report presents a more

comprehensive look at the primary outcome and at preexisting risk factors that may alter the benefit of prenatal surgery and be associated with the reduction in the need for shunting.

In this analysis, we have shown that the degree of hydrocephalus at the time of screening (19–25 weeks) has a significant impact on the effect of prenatal surgery. This is consistent with previously published studies prior to MOMS, which suggested that shunting is rarely avoided in patients with moderately to severely enlarged ventricles at the time of prenatal screening.[4] T he finding a lso has implications with regard to the timing of prenatal intervention and the counseling of prospective candidates. We know that the ventricles in a fetus with spina bifida tend to enlarge during gestation.[2] By extension, it is likely that fetuses younger than 20 weeks have even smaller ventricles. Therefore, it is possible that intervention even earlier in gestation than 20 weeks might further improve outcomes. With improvements in prenatal imaging and endoscopic technology, it might be possible to reduce the age at which intervention is feasible. With respect to counseling, the fetus with ventricles < 10 mm is clearly the ideal candidate for in utero intervention. More caution should be advised in predicting the outcome in a fetus with larger ventricles: for those whose ventricles are 15 mm or larger at screening, there appears to be no benefit related to shunting. Possible benefits independent of the effect on hydrocephalus might emerge, but this awaits further long-term analysis.

Previous literature has suggested that there is a correlation between the level of the myelomeningocele lesion and the need for shunting, whether surgery is prenatal or postnatal.[4,10] It is surprising, then, that there were no statistical differences between the rates of shunting based on lesion level at screening in either group. Therefore, lesion level would appear not to be as good a predictive tool for future shunting as ventricular size. It may be useful to perform a more detailed postnatal analysis correlating lesion level and degree of hindbrain herniation with the need for a shunt, but the current data do not support the use of lesion level or degree of hindbrain herniation to predict need for shunting during prenatal counseling.

If it is true that hydrocephalus tends to progress in the spina bifida patient during gestation, then it might be expected that operating earlier in gestation, when the hydrocephalus is less advanced, might reduce the eventual need for shunting. This has been suggested by previous studies that showed that intrauterine repair after 26 weeks of age conferred much less benefit than surgery performed between 20 and 24 weeks.[4] Our result that gestational age after adjustment for ventricle size was not significant for predicting shunt placement may simply reflect the small numbers in each group and/or the relatively small difference in gestational age between the youngest and oldest fetus who received the prenatal surgery.

The results above offer valuable insights into differences in the nature and severity of hydrocephalus between the pre- and postnatal surgery groups after birth. They also shed light on the criteria that a pediatric neurosurgeon uses in making a decision to perform shunt insertion. When MOMS was in its planning stages, an attempt was made to create a standardized set of criteria for shunt placement that would be readily acceptable to the average pediatric neurosurgeon and at the same time be verifiable by a panel of unbiased outside observers. The concern was that the threshold for placement of a shunt might be

lower for those who had received postnatal surgery. As it turns out, there were a significant number of patients in both the prenatal and postnatal groups who met criteria dictated by the MOMS protocol but did not undergo shunt placement. This confirms the importance of the blinded adjudication process in the MOMS trial. Analysis of the criteria actually used by treating neurosurgeons to make a decision whether to perform shunt treatment suggests that as a group they relied much more heavily on overt signs of increased intracranial pressure rather than progressive ventriculomegaly alone. Thus, Criteria 1b and 2–4 provided the rationale for shunting in most of the cases in each group. Criteria 1a, c, and d, which can develop in the absence overt clinical signs of increased pressure, were less likely to be used to justify placement of a shunt. It can be argued that this reflects a current trend among pediatric neurosurgeons to allow the ventricular system to enlarge to a greater extent before placement of a shunt. This strategy, which differs from what was common practice in decades past,[3,5] likely reflects an aversion to shunting and its attendant risks, but it may also, in part, be due to the recent increase in popularity of endoscopic third ventriculostomy and choroid plexus coagulation (ETV-CPC) for the treatment of hydrocephalus secondary to spina bifida (see next paragraph). In an analysis of premature infants with ventriculomegaly and/or hydrocephalus due to high-grade intraventricular hemorrhage, the investigators of the Hydrocephalus Clinical Research Network found that head circumference did not predict the need for placement of either a ventricular reservoir or subgaleal shunt, but fontanelle status did.[11] Later, the same group also showed a high interrater reliability among surgeons assessing an infant for clinical signs such as bulging fontanelle and split sutures.[13] A set of shunt criteria recently developed at University of Arkansas specifically for patients with spina bifida also suggests that a bulging fontanelle is one of the most powerful predictors of the need for a shunt.[7] Our revised criteria are in accordance with these findings and may be of use for children who will undergo prenatal surgery in the future.

Over the last 5 years, ETV-CPC has become an increasingly popular first-line treatment for hydrocephalus-associated spina bifida.[8] Accumulating data indicate that this treatment can control hydrocephalus in up to 60% of spina bifida patients.[12] The criteria for ETV-CPC may be somewhat different from those for shunt treatment and more in line with criteria that are reliant on overt clinical signs of increased intracranial pressure as mentioned above. That is to say, those who perform ETV-CPC are generally more dependent on clinically obvious signs of increased intracranial pressure, such as a bulging fontanelle or split sutures, in making their decision. They also might be more inclined to allow the ventricular size and head circumference to drift upward before intervening, as this reduces the difficulty of the procedure. It has been reported by several centers that their rate of shunt treatment in cases of spina bifida is declining even in the patient who undergoes treatment postnatally. One article stated that shunt placement is reserved “for children with symptoms, massive hydrocephalus, or significant progressive ventriculomegaly after back closure.”[5] These criteria are seconded in an article from Children’s Memorial Hospital in Chicago.[3] This declining shunt rate has been used as an argument against prenatal intervention given the risks associated with intrauterine repair. However, it is our opinion that this declining shunt rate for patients with spina bifida in general does nothing to diminish the improvements seen after intrauterine repair. As discussed above, both groups (pre- and postnatal) were equivalent at the time of screening and both were treated according to standard criteria.

Thus, any decline in shunt rate based on postnatal criteria would be expected to apply to both groups. A more accurate conclusion might be that if the rate of shunt-dependent hydrocephalus can be reduced by intrauterine repair, reduced further by narrowing the criteria for shunting, and then reduced even more by ETV-CPC, the overall need for shunting in spina bifida might also be markedly reduced going forward.

Conclusions

Of the readily identifiable prenatal factors that might predict the future need for shunt placement, only ventricular size was associated with the need for shunting. Care should be exercised in predicting beneficial effects on the need for shunting after prenatal surgery in patients with ventricles 15 mm or larger at the time of initial screening. Pediatric neurosurgeons today are more likely to rely on overt clinical signs of increased intracranial pressure by assessment of the anterior fontanelle or bony suture than traditional radiological signs of ventriculomegaly or head circumference before treating hydrocephalus. Postnatal criteria for surgical intervention for hydrocephalus are evolving, especially with the introduction of ETV-CPC as a viable alternative to shunting in these patients.

Acknowledgments

Supported by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): U10-HD041666 (Adzick), U10-HD041667 (Brock), U10-HD041669 (Farmer), and U01-HD041665 (Thom).

Comments and views of the authors do not necessarily represent views of the NICHD.

We wish to acknowledge the Shunt Outcome Review Committee (D. Douglas Cochrane, MD; James Drake, MD; John Kestle, MD; Jerry Oakes, MD; and Gilbert Vezina, MD) for assistance with the protocol and primary outcome review and Dr. Catherine Spong for protocol development and oversight.

Other participants in the MOMS trial were as follows: The Children's Hospital of Philadelphia, Pennsylvania: Lori Howell, RN, MS; Alan Flake, MD; Holly Hedrick, MD; Jamie Koh, RN, MSN; Jack Rychik, MD; Natalie Rintoul, MD; Julie Moldenhauer, MD; R. Douglas Wilson, MD; Beverly Coleman, MD; David Cohen, MD; Patrick Pasquariello, MD; and Larissa Bilaniuk, MD. University of California, San Francisco, California: Michael Harrison, MD; Hanmin Lee, MD; Jody Farrell, RN, MSN; Tamara Ryan, RN; and Rachel Perry, RN. Vanderbilt University Medical Center, Nashville, Tennessee: John Brock III, MD; Mary Dabrowiak, RN, MSN; Katharine Wenstrom, MD; Joseph Bruner, MD; Edmund Yang, MD, PhD; Nancy Chescheir, MD; and Tracy Perry. The Biostatistics Center, George Washington University, Washington, DC: Erin Greenbaum Musok, MA; and Kristen Holloway, MS. *The Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, Maryland: Catherine Y. Spong, MD; and Rosemary Higgins, MD.

Abbreviations

ETV-CPC	endoscopic third ventriculostomy and choroid plexus coagulation
MOMS	The Management of Myelomeningocele Study

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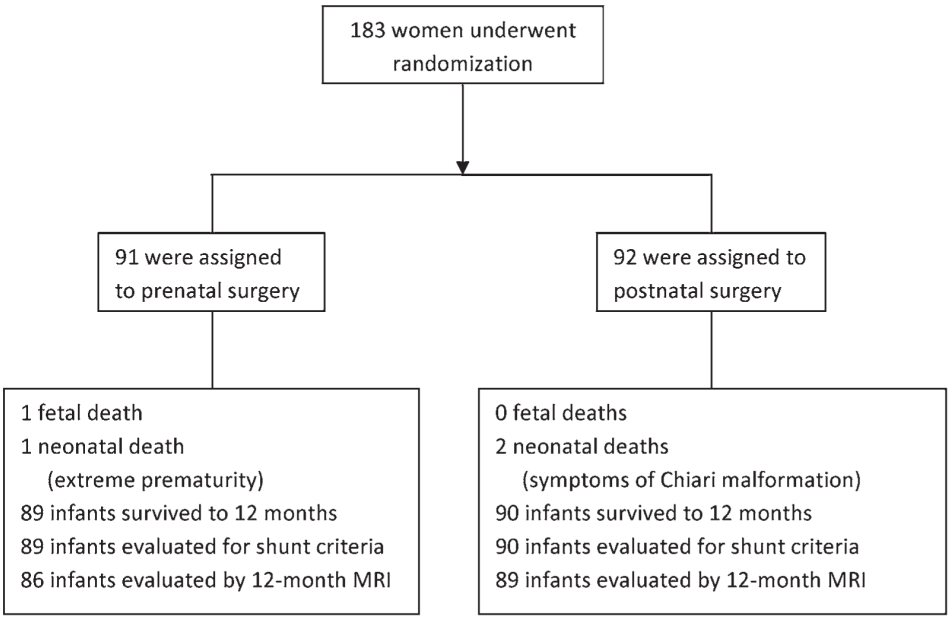

Fig. 1.
CONSORT (Consolidated Standards for Reporting of Trials) flow diagram.

TABLE 1

Baseline characteristics *

Variable	Prenatal Surgery (n = 91)	Postnatal Surgery (n = 92)
Mean gestational age at randomization in wks	23.7 ± 1.4	23.9 ± 1.3
Gestational age at randomization in wks		
<24	51 (56.0)	43 (46.7)
≥24	40 (44.0)	49 (53.3)
Mean maternal age at screening in yrs	29.2 ± 5.2	28.7 ± 4.8
Maternal race/ethnicity		
White non-Hispanic	85 (93.4)	86 (93.5)
Black non-Hispanic	1 (1.1)	1 (1.1)
Hispanic	3 (3.3)	4 (4.3)
Other	2 (2.2)	1 (1.1)
Married	84 (92.3)	86 (93.5)
Maternal yrs of schooling	14.9 ± 1.7	14.9 ± 1.7
Fetal sex female	42 (46.2)	57 (62.0)
Lesion level L-3 or lower	62 (68.1)	76 (82.6)
Lesion level (range)	L-4 (T9–S1)	L-4 (T12–S1)
Ventricle size in mm †		
<10	30 (33.0)	34 (37.0)
10 up to 15	42 (46.2)	50 (54.3)
≥15	19 (20.9)	8 (8.7)
Median ventricle size in mm (range)	11.4 (3.3–22.8)	10.5 (4.3–18.6)
Degree of hindbrain herniation		
Mild/moderate	64 (70.3)	69 (75.0)
Severe	27 (29.7)	23 (25.0)

* Data presented as number of patients (%) unless stated otherwise. Mean values are presented as the mean ± SD.

† Ventricular measurements were made via ultrasound study using the ventricle on the downside, or further from the transducer.

TABLE 2

Primary outcome and related outcomes *

Variable	Prenatal Surgery (n = 91)	Postnatal Surgery (n = 92)	Relative Risk (CI)	p Value
Primary outcome	66 (72.5)	90 (97.8)	0.74 (96.2% CI 0.65–0.85)	<0.0001
Death before shunt criteria could be evaluated	2 (2.2)	0 (0.0)		
Met criteria, shunt placed	40 (44.0)	73 (79.3)		
Did not meet criteria, shunt placed	0 (0.0)	4 (4.3)		
Met criteria, no shunt placed	24 (26.4)	13 (14.1)		
Did not meet criteria, no shunt placed	25 (27.5)	2 (2.2)		
Specific criteria met †				<0.0001
None	27 (29.7)	6 (6.5)		
Criterion 1a, c, or d only	36 (39.6)	20 (21.7)		
Criterion 1b & one or more of 1a, 1c, 1d only	21 (23.1)	35 (38.0)		
Criterion 2 (w/ or w/o Criterion 1)	0 (0.0)	2 (2.2)		
Criterion 3 (w/ or w/o Criterion 1 or 2)	6 (6.6)	6 (6.5)		
Criterion 4 (w/ or w/o Criteria 1–3)	1 (1.1)	23 (25.0)		
Revised composite outcome	45 (49.5)	80 (87.0)		<0.0001
Death before shunt criteria could be evaluated	2 (2.2)	0 (0.0)		
Met criteria, shunt placed	25 (27.5)	63 (68.5)		
Shunt placed w/o meeting criteria	15 (16.5)	14 (15.2)		
Met criteria, no shunt placed	3 (3.3)	3 (3.3)		
Did not meet criteria, no shunt placed	46 (50.5)	12 (13.0)		
Shunt & revision	14 (15.4)	37 (40.2)	0.38 (95% CI 0.22–0.66)	<0.001
No. of revisions ‡				
0	26 (65.0)	40 (52.0)		
1	7 (17.5)	21 (27.3)		
≥2	7 (17.5)	16 (20.8)		

* Data presented as number (%).

† Criterion 1: at least 2 of the following:

- **a.** an increase in the greatest occipital-frontal circumference adjusted for gestational age defined as crossing percentiles (if a plateau was reached this did not qualify);
- **b.** bulging fontanelle or split sutures or sunsetting sign;
- **c.** increasing hydrocephalus on consecutive imaging studies determined by increase in ratio of biventricular diameter to biparietal diameter according to the method of O'Hayon et al.; or
- **d.** head circumference > 95th percentile for gestational age.

Criterion 2: presence of marked syringomyelia with ventriculomegaly.

Criterion 3: ventriculomegaly with symptoms of Chiari malformation (stridor, swallowing difficulties, apnea, bradycardia).

Criterion 4: persistent CSF leakage from the myelomeningocele wound or bulging at the repair site.

‡Of those who had shunts placed.

TABLE 3

Subgroup analyses for shunt placement and outcome with revised criteria

	Shunt Placement			Revised Composite Outcome*		
Variable	**Prenatal Surgery (n = 91)**	**Postnatal Surgery (n = 92)**	**p Value†**	**Prenatal Surgery (n = 91)**	**Postnatal Surgery (n = 92)**	**p Value†**
Lesion level			0.19			0.30
T1–L2	11/29 (37.9)	15/16 (93.8)		15/29 (51.7)	16/16 (100)	
L3–S1	29/62 (46.8)	62/76 (81.6)		30/62 (48.4)	64/76 (84.2)	
Gestational age at randomization in wks			0.03‡			0.01‡
≤23	16/51 (31.4)	37/43 (86.1)		18/51 (35.3)	39/43 (90.7)	
≥24	24/40 (60.0)	40/49 (81.6)		27/40 (67.5)	41/49 (83.7)	
Ventricle size in mm			0.01‡			0.007‡
<10	6/30 (20.0)	27/34 (79.4)		6/30 (20.0)	28/34 (82.4)	
10 up to 15	19/42 (45.2)	43/50 (86.0)		22/42 (52.4)	45/50 (90.0)	
≥15	15/19 (79.0)	7/8 (87.5)		17/19 (89.5)	7/8 (87.5)	
Hindbrain herniation			0.53			0.49
Mild/moderate	27/64 (42.2)	56/69 (81.2)		28/64 (43.8)	58/69 (84.1)	
Severe	13/27 (48.2)	21/23 (91.3)		17/27 (63.0)	22/23 (95.7)	

*Revised composite outcome is defined as follows:

Shunt placement or death or meeting revised criteria as follows:

Criterion 1: bulging fontanelle or split sutures or sunsetting sign with at least 1 of the following:

a. increase in the greatest occipital-frontal circumference adjusted for gestational age defined as crossing percentiles (if a plateau was reached this did not qualify);

b. increasing hydrocephalus on consecutive imaging studies determined by increase in ratio of biventricular diameter to biparietal diameter according to the method of O'Hayon et al.; or

c. head circumference > 95th percentile for gestational age.

J Neurosurg Pediatr. Author manuscript; available in PMC 2017 January 03.

Criterion 2: presence of marked syringomyelia with ventriculomegaly.

Criterion 3: ventriculomegaly with symptoms of Chiari malformation (stridor, swallowing difficulties, apnea, bradycardia).

Criterion 4: persistent CSF leakage from the myelomeningocele wound or bulging at the repair site.

[†] p value for interaction between factor and surgery group by logistic regression adjusting for sex and lesion level.

[‡] Ventricle size and gestational age are included as continuous variables in the model.

TABLE 4

Association of prenatal risk factors with shunt placement and revised composite outcome in the prenatal surgery group

	Shunt Placement		Revised Composite Outcome*	
Variable	**Adjusted OR (95% CI)**	**p Value**	**Adjusted OR (95% CI)**	**p Value**
Lesion level	1.24 (0.89–1.74)	0.21	1.27 (0.89–1.81)	0.19
Gestational age at randomization	1.25 (0.83–1.88)	0.28	1.35 (0.89–2.06)	0.16
Ventricle size	1.46 (1.20–1.79)	0.0002	1.57 (1.26–1.97)	<0.0001
Severe hindbrain herniation	1.13 (0.62–2.04)	0.70	1.64 (0.87–3.08)	0.13
Fetal sex female	1.46 (0.51–4.21)	0.48	1.68 (0.55–5.09)	0.36

*Refer to Table 3 for definitions of the criteria.