Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplemental Web Appendix

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Expertise of maternal –fetal surgical teams

The maternal-fetal surgery teams at the three clinical centers had extensive experience with open maternal-fetal surgery and had performed at least fifteen fetal myelomeningocele repairs prior to the start of the trial.

Preoperative evaluation

Screening included a comprehensive anatomic and transvaginal ultrasound, fetal MRI and echocardiogram, psychosocial evaluation to ensure that the patient had adequate psychosocial support systems, and counseling by the study-approved maternal-fetal surgeon, neurosurgeon, neonatologist, anesthesiologist and maternal-fetal medicine specialist.

1. Comprehensive obstetrical ultrasound examination, including documentation of cervical length, gestational age biometry, lesion level, ventricular size, foot positioning, and lower extremity movement, in addition to a fetal echocardiogram.
2. Fetal MRI to document hindbrain herniation and screen for other brain abnormalities.
3. Maternal physical examination and clearance for surgery by the anesthesiology and the OB/GYN staff.
4. Psychosocial evaluation to identify family dynamics and social issues that would impact the family's strategies for the remainder of the pregnancy and after the birth of the child. The social worker also developed interventions if such issues were identified.
5. Teaching about neural tube defects, community resources, information regarding prenatal and postnatal surgery, management following prenatal surgery, and recommendations for continued care for the postnatal group.
6. A focused interview to afford potential participants a formal opportunity to examine what they learned about the research study in the course of their evaluation and to discuss how they feel about enrolling in the research study.

Prenatal Surgery Procedure:

Cephazolin (1000 mg IV) and indomethacin (50 mg PR or PO) were given preoperatively. A combination of general and epidural anesthesia was used. The indwelling epidural catheter enabled administration of continuous postoperative analgesics. The gravid uterus was exposed via a low transverse laparotomy incision and exteriorized. A vertical skin incision was used in patients with a BMI>30 or those with a previous vertical skin scar. The fetus and placenta were then located by ultrasound and the hysterotomy location chosen by the primary surgeon. The fetus was visualized by ultrasound and manually positioned within the uterus such that the myelomeningocele sac was in the center of the hysterotomy. In the case of an anterior placenta, hysterotomy was either fundal or posterior. In the case of a posterior placenta, uterine entry was anterior. Under sonographic guidance, the surgeon placed two monofilament traction sutures through the full thickness uterine wall, initial uterine entry was accomplished sharply between the uterine traction sutures, then the uterine stapling device loaded with absorbable polyglycolic acid staples (Covidien Auto Suture, Norwalk CT) was passed into the uterine cavity. The stapler was palpated manually and ultrasonography was used to exclude the presence of fetal tissue, then the stapler was used to create a 6-8 cm uterine incision large enough to expose the fetal myelomeningocele. The fetus was given an intramuscular injection of fentanyl (20 mcg/kg) and vecuronium (0.2mg/kg). During the procedure, the fetal cardiac function was monitored with continuous echocardiography by an individual not involved in the actual prenatal surgery.

The myelomeningocele was closed in a standardized manner under magnification. The neural placode was sharply dissected from surrounding tissue and allowed to drop into the spinal canal. The dura was then identified, reflected over the placode and then closed using a fine running suture. If there was insufficient dura for closure, Duragen (Integra Life Sciences Corporation, Plainsboro, NJ) was substituted. If it was not possible to obtain skin closure, relaxing incisions were made or Alloderm (Life Cell, Branchburg, NJ) was used. Finally, the skin was mobilized and closed using a fine running monofilament suture.

The uterus was closed in two layers. The first layer incorporated the absorbable staples and uterine membranes. As the last stitches of this layer were placed, warmed Ringer's lactate, mixed with 500 mg of Nafcillin or vancomycin, was added to the uterus until the amniotic fluid index was normal. A second imbricating layer of suture was tied**.** The abdominal fascial layer and dermis were closed in routine fashion.

Prenatal Surgery Patient Management postoperatively and during remaining pregnancy:

Cephazolin (1 gram every 6 hours for a total of 4 doses) was continued postoperatively. Intravenous magnesium sulfate (6 gram loading dose; then 2-4 g/hr) was started in the operating room after uterine closure, and continued for the first 18 to 48 hours following surgery. Indomethacin was given as a 50 mg (PR or PO) preoperatively, followed by 50 mg (PR or PO) every 6 hours for the first 24 hours following surgery and 25 mg every 6 hours on the second day. During the two days that the mother was on indomethacin, a fetal echocardiogram was performed each day to evaluate cardiac function and assess constriction of the ductus arteriosus. Maintenance therapy consisted of oral nifedipine (10-20 mg every 4-6 hours) and was continued until 36 weeks 6 days. First line tocolysis was re-initiated when there were palpable, uncomfortable contractions occurring preterm for longer than one hour, and at a frequency of greater than or equal to 4 per 20 minutes. Magnesium sulfate was the primary tocolytic in such cases.

Since prenatal surgery patients are at increased risk of preterm labor, use of tocolytics was planned until 36^{6} weeks gestation. All patients stayed in the hospital until they were on a regular diet, had return of bowel function, were able to ambulate to the bathroom without assistance, demonstrated good tocolytic control, and had good postoperative pain management on oral medications. All discharged patients (and their support person) remained close to the fetal surgery clinical center in accommodations provided to permit standardized postoperative management, ultrasound evaluation, and delivery. They were on modified bedrest for the first two weeks post discharge, then subsequently allowed to graduate to moderate activity if the uterus remained quiescent.

Outpatient follow-up was scheduled every week. In addition to the usual content of a prenatal visit, maternal assessment included the degree of postoperative discomfort, wound healing, and premature labor/delivery risks. A brief "targeted" ultrasound was performed to assess amniotic fluid volume and membrane status since oligohydramnios and chorioamniotic membrane separation are the most frequent complications following maternal-fetal surgery and their presence may directly impact pregnancy management. Fetal well-being was determined at every visit after 25 weeks by means of a biophysical profile. Comprehensive ultrasonography was performed monthly to measure: biparietal diameter, head circumference, femur length, abdominal circumference, amniotic fluid index and maximum vertical pocket, status of the chorion, and ventricular size.

Recurrent late, prolonged or severe variable fetal heart rate decelerations, or a sinusoidal pattern, or prolonged bradycardia were sufficient grounds for delivery if conservative measures, such as maternal position change, administration of oxygen, and intravenous fluid hydration were unsuccessful.

Oligohydramnios was managed in the hospital, with fetal heart rate or non-stress test assessment every nursing shift when the amniotic fluid index was less than 5cm. When chorioamniotic membrane separation was seen by ultrasound, patients were placed on bedrest with bathroom privileges only. If the

membrane separation progressed and extended to the placental cord insertion site, patients were admitted and placed on bed rest, and a fetal heart rate strip was obtained every shift or if decreased fetal movement is observed.

If the patient experienced preterm labor unresponsive to tocolytic therapy, chorioamnionitis, suspected uterine rupture, placental abruption or a non-reassuring fetal status, she was delivered via cesarean section. If the patient experienced rupture of membranes at less than 34 weeks gestation, she was treated expectantly until 34 weeks of gestation at which time she was delivered via cesarean.

Corticosteroids were not used at the time of antenatal surgery, but only in the case of threatened preterm delivery prior to 34 weeks. If preterm labor was diagnosed and the likelihood of delivery was high (e.g., there was premature membrane rupture, vaginal bleeding, or nonreassuring antepartum fetal surveillance), a single course of steroid therapy was given to minimize complications of prematurity.

At 37 weeks gestation, delivery was by cesarean. Delivery by cesarean was necessitated by the presence of the hysterotomy scar. Although the same abdominal incision was used for the cesarean as for the prenatal surgery, the fetus was preferably delivered via a lower uterine segment incision.

Criteria for shunt placement

1. At least two of the following:
   - An increase in the greatest occipital-frontal circumference adjusted for gestational age defined as crossing percentiles. Patients who cross centiles and subsequently plateau do not meet this criteria
   - A bulging fontanelle (defined as above the bone assessed when the baby is in an upright position and not crying) or split sutures or sunsetting sign (eyes appear to look downward with the sclera prominent over the iris)
   - 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. (O'Hayon BB, Drake JM, Ossip MG, et al. Frontal and occipital horn ratio: a linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. Pediatr Neurosurg.1998; 29:245 –9).
   - Head circumference > 95th percentile for gestational age

or

2. Presence of marked syringomyelia (syrinx with expansion of spinal cord) with ventriculomegaly (undefined).

or

3. Ventriculomegaly (undefined) and symptoms of Chiari malformation (stridor, swallowing difficulties, apnea, bradycardia)

or

4. Persistent cerebrospinal fluid leakage from the myelomeningocele wound or bulging at the repair site

The study neurosurgeon at each center was responsible for contacting the baby's neurosurgeon to explain the trial and the criteria for shunting. A standardized letter was used to outline the study criteria for shunting and to request that the community neurosurgeon contact the study neurosurgeon if it appeared that a shunt was required.

All babies were reviewed after one year of age by a central blinded adjudication process to determine whether the shunt criteria had been satisfied.

Detailed Inclusion Criteria

1. Myelomeningocele (including myeloschisis) at level T1 through S1 with hindbrain herniation. Lesion level confirmed by ultrasound and hindbrain herniation confirmed by MRI at the MOMS Center.
2. Maternal age ≥18 years
3. Gestational age at randomization of 19^0 to 25^6 weeks gestation as determined by clinical information and evaluation of first ultrasound. If the patient's last menstrual period (LMP) is deemed sure and her cycle is 26 to 32 days, and if the biometric measurements from the patient's first ultrasound confirm this LMP within the ranges in the table below, the LMP will be used to determine gestational age. In all other cases (i.e. if the LMP is unsure, if she has an irregular cycle or her cycle is outside the 26-32 day window or if the measurements from her first ultrasound are discrepant from the ultrasound as detailed below), the ultrasound determination will be used. Once the EDC has been determined for the purposes of the trial, no further revision is made.

Gestational age at first ultrasound by LMP	Ultrasound agreement with LMP
up to 19^6 weeks	$\pm$7 days
20^0 weeks or more	$\pm$14 days

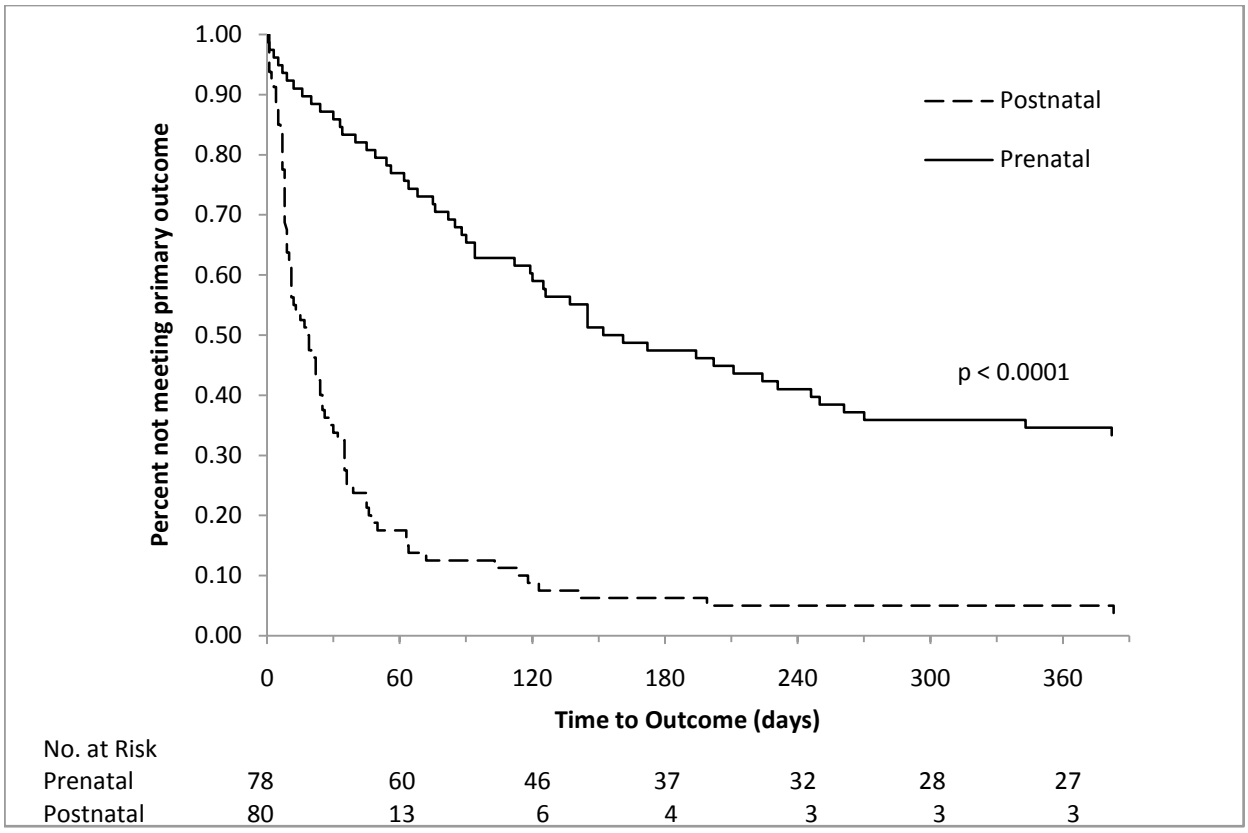
4. Normal karyotype with written confirmation of culture results. Results by fluorescence in situ hybridization (FISH) will be acceptable if the patient is at 24 weeks or more.

Detailed Exclusion Criteria

1. Non-resident of the United States.
2. Multifetal pregnancy.
3. Insulin dependent pregestational diabetes.
4. Fetal anomaly not related to myelomeningocele. A fetal echocardiogram will be conducted before randomization and if the finding is abnormal, the patient will be excluded.
5. Kyphosis in the fetus of 30 degrees or more.
6. Current or planned cerclage or documented history of incompetent cervix.
7. Placenta previa or placental abruption.
8. Short cervix < 20 mm measured by cervical ultrasound. The patient may be excluded based on an ultrasound report during initial screening or based on the cervical length measurement performed at the MOMS center as part of the final evaluation.
9. Obesity as defined by body mass index of 35 or greater.
10. Previous spontaneous singleton delivery prior to 37 weeks.

11. Maternal-fetal Rh isoimmunization, Kell sensitization or a history of neonatal alloimmune thrombocytopenia.
12. Maternal HIV or Hepatitis-B status positive because of the increased risk of transmission to the fetus during maternal-fetal surgery. If the patient's HIV or Hepatitis B status is unknown, the patient must be tested and found to have negative results before she can be randomized.
13. Known Hepatitis-C positivity. If the patient's Hepatitis C status is unknown, she does not need to be screened.
14. Uterine anomaly such as large or multiple fibroids or mullerian duct abnormality.
15. Other maternal medical condition which is a contraindication to surgery or general anesthesia. This includes any patient with a previous hysterotomy in the active segment of the uterus (whether from a previous classical cesarean, uterine anomaly such as an arcuate or bicornuate uterus, major myomectomy resection, or previous fetal surgery).
16. Patient does not have a support person (e.g., husband, partner, mother).
17. Inability to comply with the travel and follow-up requirements of the trial.
18. Patient does not meet other psychosocial criteria (as determined by the psychosocial interviewer using a standardized assessment) to handle the implications of the trial.
19. Participation in another intervention study that influences maternal and fetal morbidity and mortality or participation in this trial in a previous pregnancy.
20. Maternal hypertension which would increase the risk of preeclampsia or preterm delivery (including, but not limited to: uncontrolled hypertension, chronic hypertension with end organ damage and new onset hypertension in current pregnancy).

Figure: Time to Meeting Criteria for the First Primary Outcome



No. at Risk							
Prenatal	78	60	46	37	32	28	27
Postnatal	80	13	6	4	3	3	3

Adverse Events

Serious, common and important adverse events are reported in the outcome tables (Tables 2 - 4). These include: fetal, neonatal and infant death, chorioamniotic separation, spontaneous membrane rupture, oligohydramnios, pulmonary edema, chorioamnionitis, placental abruption, uterine dehiscence, spontaneous labor, dehiscence of the fetal or neonatal surgical repair, necrotizing enterocolitis, pneumothorax, periventricular leukomalacia (PVL) epidermoid cyst, Chiari decompression and shunt infection.

The following adverse events were also reported in the cohort randomized before 07/01/09 (158 patients)

	Prenatal repair (n=78)	Postnatal repair (n= 80)
Maternal		
Lower quadrant pain following prenatal surgery	4 (5.1%)	0 (0.0%)
Subchorionic hemorrhage	1 (1.3%)	0 (0.0%)
Preterm cesarean delivery for worsening hydrocephalus	0 (0.0%)	1 (1.3%)
Nephrolithiasis	1 (1.3%)	0 (0.0%)
Preterm contractions following motor vehicle accident	0 (0.0%)	1 (1.3%)
Choriocarcinoma	0 (0.0%)	1 (1.3%)
Pyelonephritis	1 (1.3%)	0 (0.0%)
Fetal/Neonatal		
Intraoperative blood transfusion at repair	0 (0.0%)	1 (1.3%)
Fetal-maternal hemorrhage	0 (0.0%)	1 (1.3%)
Laryngomalacia/vocal cord dysfunction	2 (2.6%)	0 (0.0%)
Femur fracture	3 (3.9%)	1 (1.3%)
Intraspinal mucous cyst	0 (0.0%)	1 (1.3%)

Listed below are adverse events for 25 additional women and their offspring (median follow-up from randomization 29.9 weeks) who were randomized on or after 7/1/09.

	Prenatal repair (n=13)	Postnatal repair (n= 12)
Maternal		
Oligohydramnios	3 (23.1%)	0 (0.0%)
Chorioamniotic separation	1 (7.7%)	0 (0.0%)
Hematoma at maternal incision	1 (7.7%)	0 (0.0%)
Intraoperative uterine hemorrhage	1 (7.7%)	0 (0.0%)
Preterm premature rupture of the membranes	1 (7.7%)	0 (0.0%)
Fetal/Neonatal		
Asystole at fetal surgery (recovered)	1 (7.7%)	0 (0.0%)
Bradycardia at fetal surgery	1 (7.7%)	0 (0.0%)
Pneumothorax	1 (7.7%)	0 (0.0%)
PVL	1 (7.7%)	0 (0.0%)