18 **FETAL IMMUNE SUPPRESSION AS ADJUNCTIVE THERAPY FOR IN UTERO HEMATOPOIETIC STEM CELL TRANSPLANTATION IN NON-HUMAN PRIMATES** LAURENCE SHIELDS[1], LAKSHMI GAUR[2], ROBERT ANDREWS[3]; [1]University of Washington, Obstetrics and Gynecology, Seattle, WA; [2]University of Washington, Seattle, WA; [3]Fred Hutchinson Cancer Research Center, Seattle, WA

OBJECTIVE: In utero hematopoietic stem cell transplantation (IUTx) is a therapeutic procedure that could potentially cure many diseases affecting the fetal immune and hematopoietic systems. To date, IUTx has rarely been successful due to low or infrequent engraftment and chimerism, possibly due to fetal immune rejection of donor cells. Therefore, our objective was to test the hypothesis that intense fetal immunosuppression would improve engraftment and the level of chimerism after IUTx in fetal non-human primates.

STUDY DESIGN: Female M. nemistrina fetuses (~0.35 gestation) were treated with 50 mg/kg anti-thymocyteglobulin (ATG) and 0.8 mg/kg betamethasone (BMZ) 24-hrs prior to intraperitoneal injection of purified CD34+ male allogeneic donor cells (sire). Donor cell engraftment was assessed by PCR for male specific DNA from bone marrow (BM), peripheral blood, and colony-forming cells (CFC's) from fetal liver (FL) and BM.

RESULTS: Five animals have been treated using this protocol. Two animals were delivered prematurely (0.45 and 0.80 gestation). CFC's from FL cells revealed 17.7-33.7% were of donor origin. BM CFC's from the fetus delivered at 0.80 gestation showed 35/80 (43%) were of donor origin. Of the three other animals one has delivered at term and two are still in utero. The animal delivered at term showed multilineage engraftment in hematopoietic progenitor cells, CD13 granulocytes, and CD20 lymphocytes. Evaluation of lymph nodes and thymic tissue in the animal delivered at 0.8 gestation did not show histologic abnormalities secondary to the immunosuppressive therapy.

CONCLUSION: This preliminary data supports the hypothesis that fetal immune function may be a factor limiting engraftment by allogeneic hematopoietic stem cells in the fetus. Further detailed study of these animals postnatally will be needed to determine if fetal immune suppression results in stable durable engraftment and any deleterious effects on other developing organ systems.

19 **FETAL MYELOMENINGOCELE (MMC) REPAIR: SHORT TERM OUTCOMES** MARK JOHNSON[1], NATALIE RINTOUL[2], LESLIE N SUTTON[3], TIMOTHY M CROMBLEHOLME[4], ALAN W FLAKE[2], LORI J HOWELL[2], MERLE OXMAN[2], R DOUGLAS WILSON[2], N SCOTT ADZICK[5]; [1]Children's Hospital of Philadelphia, Center for Fetal Diagnosis & Treatment, Philadelphia, PA; [2]Children's Hospital of Philadelphia, Center for Fetal Diagnosis & Treatment, Philadelphia, PA; [3]Children's Hospital of Philadelphia, Pediatric Neurosurgery, Philadelphia, PA; [4]Children's Hospital of Philadelphia, Center for Fetal Diagnosis & Treatment, Philadelphia, PA; [5]Children's Hospital of Philadelphia, Center for Fetal Diagnosis & Treatment, Philadelphia, PA

OBJECTIVE: Evaluate short term outcomes in fetuses that underwent antenatal MMC repair.

STUDY DESIGN: 41 fetuses underwent open fetal MMC closure between 20-25 wks. GA. Inclusion criteria included < 26 wks GA, thoracic to S1 level defect, normal leg movement without club feet, presence of Arnold-Chiari malformation, ventricles < 17 mm, normal karyotype, no other anomalies, and elective cesarean delivery at 36 weeks.

RESULTS: 2 patients are undelivered, 3 fetuses were lost to PTL. Of the remaining 36, mean age of delivery was 34 weeks 4 days (29-37). 36/36 (100%) have shown reversal of hindbrain herniation by fetal MRI at 6 weeks post-op. Mean pre-operative maximum ventricle size = 11.2 mm (6-17), mean post-operative maximum ventricle size = 15.9 mm (7.5-27.6), and mean maximum increase in ventriculomegaly = 5.4 mm (0.9-16.0). 22/33 (67%) of neonates had better neurologic leg function than predicted based on lesion level at birth (no difference = 9, 1 level loss = 2). 7/37 (19%, 5 single, 2 bilateral) infants have clubfoot deformity. 11/36 (30.5%) of surviving infants required ventriculoperitoneal (VP) shunting (1/3 – 33% thoracic, 9/33 – 27% lumbar, 1/4 – 25% sacral). This shunting rate compares to 100% thoracic, 88% lumbar, and 68% sacral (85% overall) V-P shunt rate in 297 non-fetal repair cases collected from the CHOP Spina Bifida Clinic.

CONCLUSION: Early experience with fetal MMC repair suggests: 1) decrease need for V-P shunting (30% versus 85% for historic postnatal repair controls), 2) arrest or slowing of progressive VM and consistent resolution of hindbrain herniation, 3) possible neurologic improvement in lower leg function. However, long-term follow-up is needed for leg, bladder, bowel and head neurodevelopment. A multicenter, randomized controlled trial is planned.

20 **INTRAUTERINE REPAIR OF SPINA BIFIDA: PREOPERATIVE PREDICTORS OF SHUNT-DEPENDENT HYDROCEPHALUS** JOSEPH BRUNER[1], NOEL TULIPAN[2], GEORGE REED[3], GEORGE DAVIS[1], LAURA STONE[1]; [1]Vanderbilt University, Obstetrics & Gynecology, Nashville, TN; [2]Vanderbilt University Medical Center, Pediatric Neurosurgery, Nashville, TN; [3]University of Massachusetts, Preventive and Behavioral Medicine, Nashville, TN

OBJECTIVE: To identify factors present prior to performance of open maternal-fetal surgery for repair of spina bifida which may predict the need for ventriculoperitoneal shunt placement.

STUDY DESIGN: All infants > 12 months old after intrauterine repair of spina bifida were studied. Potential determinants analyzed included preoperative ventricular measurements, degree of hindbrain herniation, anatomical level of the lesion, type of lesion, presence of talipes, and gestational age at repair.

RESULTS: Of 76 infants studied, 46 (60.5%) required shunts and 30 did not. Maternal age, race, gravidity and parity did not affect the need for shunt placement; neither did the type of lesion (myelomeningocele or myeloschisis), the presence/absence of talipes in the fetus, nor gestational age at delivery. The strongest predictor of shunt requirement was the upper level of the lesion: 31/34 fetuses (91%) with lesions >= L3 required shunts, compared to 15/42 fetuses (36%) with lesions <= L4 (Fisher's exact test: $P < .001$; Odds ratio = 24.6, 95% CI [4.8, 125]). In those fetuses with lesions <= L4, EGA at the time of repair was the strongest predictor: 12/24 fetuses (50%) received shunts if the EGA at repair was >= 25 weeks, compared to 3/18 fetuses when the EGA was < 25 weeks ($P = .009$; OR 6.5 [1.6, 26.8]; OR 1.5 [1.1, 2.2] for each increase in age by one week). The area under the ROC curve using these two factors = 0.8725. Size of the ventricles prior to repair and degree of hindbrain herniation both correlate highly with the level of the lesion; once adjusted for lesion level, neither is significant. Of the 18 fetuses with lesion level <= L4 and lesion closure < 25 weeks only three (16.6%) have shunts at 12 months of age.

CONCLUSION: Fetuses with spina bifida lesions at L4 or below repaired before 25 weeks' gestation are at low risk for ventriculoperitoneal shunt placement.

21 **COMBINED SECOND TRIMESTER BIOCHEMICAL AND ULTRASOUND SCREENING FOR DOWN SYNDROME IS HIGHLY EFFECTIVE** LILLIAN KAMINSKY[1], JAMES EGAN[2], JUN YING[3], ADAM BORGIDA[1], MICHAEL DEROCHE[1], PETER BENN[4]; [1]University of Connecticut, Obstetrics and Gynecology, Farmington, CT; [2]St. Francis Hospital and Medical Center, Obstetrics and Gynecology, Hartford, CT; [3]University of Connecticut, Statistics, Storrs, CT; [4]University of Connecticut, Pediatrics, Farmington, CT

OBJECTIVE: To develop a combined second trimester screen for Down syndrome (DS) using 4 marker (Quad) serum tests together with nuchal fold (NF) and biparietal diameter to humerus length (BPD/HL) ratio and/or biparietal diameter to femur length (BPD/FL) ratio.

STUDY DESIGN: Ultrasound findings at 15 to 22 weeks for 699 contol pregnancies were reviewed to determine gestational age-specific normal median NF values. The NF measurements in 37 DS cases and the controls were converted to multiples of the median. BPD/HL and BPD/FL values for 7061 control pregnancies and 68 DS cases were also established. The means, standard deviations, correlation coefficients for the Gaussian-distributed log-transformed variables were determined and used to calculate likelihood ratios. Second trimester age-specific risks for DS were modified using these likelihood ratios. Expected sensitivity (S) and false-positive rates (FPR) were determined for the 1999 US population of pregnant women using computer simulation methods.

RESULTS: Using a second trimester 1:270 cut-off, Quad plus NF can provide S = 87.4% with FPR = 4.3%. This compares with S = 81.5% and FPR = 6.9% for the current Quad test alone. Adding long bone measurements results in a further modest enhancement in performance (S = 89.0%, FPR = 3.8%). The combination of Quad, NF, BPD/HL and BPD/FL (7-parameter screening) and a 1:120 cut-off can provide S = 84% and FPR = 1.9%. For women aged 35, or more, the 7-parameter screen at the 1:120 cut-off provides S = 94.9% and FPR = 6.2%.

CONCLUSION: Combined second trimester biochemical and ultrasound screening offers a potentially significant improvement over current second trimester screening protocols. It appears to be particularly effective for advanced maternal age women. Further enhancement is likely when ultrasound detection of anatomic anomalies is considered.