

## C-Sections Continue to Make Headlines

As soon as news of Britney Spears' elective C-Section was announced, CBS asked Dr. Cathy Spong, NICHD Program Director, to appear on the September 16<sup>th</sup> Early Show to discuss the pros and cons of elective C-Section. Drawing on data from the Network's C-Section study and obstetrical knowledge, Dr. Spong compared the benefits of vaginal deliveries for the mother and baby with few risks to the increased risks related to surgery and the missed benefits of the normal labor process for the baby. She also announced that a State of the Science meeting is being planned by NICHD for 2006 to discuss the benefits and risks of C-Sections.

Prior to this event, the August 24<sup>th</sup> edition of *USA TODAY* ran an article describing how, because doctors and hospitals fear lawsuits if something goes wrong in a vaginal birth after a C-section (VBAC), women are left with no choice but to schedule a repeat cesarean. More than 90 percent of pregnant women who have had a C-section will have another, which means, as the number of primary C-section rises (currently almost 30 percent), the overall number of C-sections will continue to increase. The article claims that large teaching hospitals are becoming the only place where women can choose a VBAC.

A number of pregnant women view the VBAC bans as an attack on their personal choice. The article states that doctors and hospitals blame the ban on guidelines issued by the American College of Obstetricians and Gynecologists in 1999, which call for an "immediately available" surgical team in case a uterine rupture necessitates an emergency C-section. Hospitals claim they cannot afford to have an anesthesiologist and operating room available whenever a patient attempts a VBAC. The article also cites the results of the Network's C-section study that found ruptures occurred in fewer than one percent of those who chose to have a VBAC. As a result of the ban, many women are choosing to have a home delivery or deciding to travel, if possible, to an academic medical center where VBACS are allowed.



## Central Readings of BEAM Ultrasounds Finish

The BCC staff and Drs. Bulas, Seibert, and DiPietro conducted the last of the central reviews of cranial ultrasounds from the BEAM trial on September 19 and 20. The team has met fourteen times over the past five years and has read more

than 7,000 ultrasounds. Dr. Thom hosted a celebratory dinner in her home for the doctors along with BCC and NICHD staff. The contributions of these radiologists to the success of the BEAM trial are much appreciated by all. The group's teamwork, conviviality and lunches together in the cafeteria at the Children's National Medical Center where the readings were performed, will be missed



*Radiologists for BEAM Central Reviews: Drs. Mike DiPietro (U. of Michigan), Dorothy Bulas (National Children's Hospital) and Joanne Seibert with recent rotator cuff surgery (U. of Arkansas)*

## MFMU Trials Duly Registered by Deadline

In compliance with the International Committee of Medical Journal Editors (ICMJE), all ongoing NICHD MFMU Network trials have been registered on the NIH ClinicalTrials.gov web site. Representing major medical journals such as *JAMA*, the *New England Journal of Medicine*, *The Lancet*, *The Annals of Internal Medicine*, and MEDLINE, the ICMJE published a joint editorial last September aimed at promoting the registration of all federal and private clinical trials.

It stated that they will consider a trial for publication in their journals only if it has been publicly registered before the enrollment of the first patient (for trials starting recruitment on or after July 1, 2005). For ongoing trials, registration was required before September 13, 2005. Many other journals and governments are following suit.

In order for a trial to be registered in accordance with ICMJE policy, a data set of twenty items describing the trial must be completed using "informative terminology". The registry also must be electronically searchable and accessible to the public at no charge. By registering the NICHD MFMU Network clinical trials on ClinicalTrials.gov, these requirements are fulfilled.



## Placental Analysis Scheduled for FVL and BEARS Placentas

With a combined total of more than 650 placentas from both of the FVL and BEARS studies, NICHD requested the submission of analysis proposals from Network investigators to utilize these samples. Since both of these studies were concluded several years ago, the NICHD wants to stimulate the use of this resource. The proposals were distributed to and prioritized by the SC by secret ballot following the July Steering Committee meeting. Following is a brief overview of the funded proposals.



*A Survey of Placental Alterations Associated with Inherited*

*Hypercoagulable States*, submitted by Drs. Wendel and Rogers at UTSW, will evaluate placentas collected in the Factor V Leiden study. The analysis will evaluate the frequency of fetal thrombotic lesions with Factor V Leiden mutation, controlling for clinical conditions and pathologic evaluation. At the same time, the thrombophilic state of the fetus will be evaluated to assess from transfer of the tendency for thrombophilia to the fetus.

Using placentas from the BEARS trial, Drs. Mercer and Sawady at Case Western Reserve University will evaluate the acute effects of repeated antenatal corticosteroids (ACS) to determine if the effects are more pronounced in those deliveries closer to the last ACS administration in their study, *The Impact of Repeated Antenatal Corticosteroids on Placental Growth and Development*. In addition, they hope to determine the effect of repeated ACS on placental growth and markers of development and inflammation and to assess where or not repeated ACS are expressed differently depending on gestational age.

Drs. Margaret Harper and Heather Mertz of Wake Forest University will study placentas from the BEARS trial. Their hypothesis, based on research which has shown that endothelial nitric

oxide synthase is a mediator of placental blood flow in the fetus, is that betamethasone exposure influences fetal growth through a nitric oxide mediated mechanism.

Placental studies that were proposed and not funded during this round may be considered in the future if funds are available. If no funding is needed, investigators should proceed along the typical secondary analysis track and submit their requests to the appropriate subcommittee(s) for approval and prioritization.

## NICHD Prenatal Screening Workshop: Incorporating the First Trimester Studies

In December of 2004, the NICHD convened a workshop, *Prenatal Screening: Incorporating the First Trimester Studies*. The August 2005 issue of *Seminars of Perinatology* features the papers presented at the workshop. Drs. Michael Mennuti and Uma Reddy are the guest editors of this edition. The workshop included experts in the fields of obstetrics, maternal-fetal medicine, radiology, genetics, pediatrics,

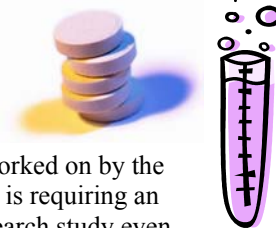


epidemiology, ethics, and public health. The goal of the workshop was to examine and discuss the research on first and second trimester screening for fetal aneuploidy and discuss the impact of clinical implementation of various combinations of screening tests. The articles highlight the development and contribution of different components of screening for the detection of aneuploidy; the role of invasive testing; recent U.S. studies; the economic consequences of first trimester screening; and the ethical issues surrounding Down syndrome screening. A major focus of the discussion was on improving risk assessment for patients so that invasive diagnostic procedures and subsequent

losses can be minimized. Of particular note are articles by MFMU Network Principal Investigators, Dr. Fergal Malone, *Nuchal Translucency-Based Down Syndrome Screening: Barriers to Implementation*, and Dr. Ron Wapner, co-authored with Dr. Mark Evans, on a study coordinated by the BCC, *First Trimester Screening: The BUN Study and Invasive Prenatal Diagnostic Procedures 2005*. The issue may be found through <http://www.sciencedirect.com/science>

## Work Continuing to Bring Up TSH Trial

The Steering Committee voted at the July Steering Committee meeting officially to refer to the upcoming trial, A Randomized, Placebo-controlled Trial of Thyroxine Therapy for Subclinical Hypothyroidism Diagnosed During Pregnancy on Subclinical Hypothyroidism as TSH, which serves double duty as an acronym because in this study TSH (thyroid stimulating hormone) levels are being monitored in pregnant women. The BCC is continuing to work on the protocol, data forms and manual of operations. The MFMU Data and Safety Monitoring Committee will provide a critical review of the protocol during a conference call scheduled for December 8. Meanwhile, the BCC is soliciting bids for a central laboratory to provide screening tests of TSH and free T4 levels (if TSH levels are elevated) in approximately 150,000 pregnant women, in addition to monthly testing of TSH and T4 levels in all enrolled patients (about 1500) and TSH in infants at delivery. Total T4, thyroid peroxidase antibodies (TPO) and urinary iodine excretion also will be measured. Details regarding the study medications, packaging and distribution are also being worked on by the BCC. The FDA is requiring an IND for this research study even though thyroxine currently is given to pregnant women.



## CAPPS RCT Maintains Monthly Target

Recruitment into the CAPPS trial, which is maintaining a steady pace of about 250 patients a month, now stands at over 4,000. At this rate, it is estimated that the trial will recruit the remaining 6,000 patients in about two more years. However, in order to finish the Prediction part of this trial at the same time, 150 of the 250 trial patients also need to agree to be in this study each month (a 60% consent rate). Meanwhile, it has been reported that a similar trial in Britain has just wrapped up enrollment with 2,400 high-risk patients (the Network trial has low-risk only). A Canadian trial, also studying anti-oxidants and preeclampsia in low-risk patients, has been reported as having enrollment difficulties.

Two additional persons, Karen Dorman and Gail Mallett, have volunteered to help with the CAPPS chart reviews, thus making a total of three teams. For this study, the medical charts of all patients who have an elevated blood pressure, a 2+ urine protein dipstick, proteinuria, or suspected or diagnosed to have preeclampsia, are being reviewed centrally. It is estimated that approximately 1,000 charts will be examined by the end of the trial. To expedite the process, the BCC has begun entering the revised data that result from the chart inspections into the computer data base and, at the same time, notifying the centers to correct their data.

The BCC has initiated procedures to submit an application to NICHD for a Certificate of Confidentiality for the CAPPS Prediction study on behalf of all the centers in the Network. This action is the result of the IRB decision at UTSW not to approve the CAPPS Prediction protocol without a Certificate because paternal DNA is being collected as part of the study. The application requires special language in the patient's informed consent form, IRB approval of the Certificate, the IRB's OHRP authorization number and official sign

off by the Network PI and authorized institutional officials. It is anticipated that most of the Network protocols in the future will involve Certificates of Confidentiality because of the sensitive nature of patient data that are collected.

The BCC is pleased to report that the expired drug exchange between all the centers and Eminent Services proceeded smoothly in early August. Satisfactory results from tests on the fatty acid capsules used for the Omega-3 trial resulted in the postponement of a drug exchange for at least a year

## GDM Trial Grabs Notice

The summer months have seen a dramatic increase in the number of randomized patients and, as a result, half of the sample size for Groups 1 and 2 has now been recruited (950)! Sixty-two patients were randomized/enrolled in August, fifty-four in June and 37 in July, for a 3-month average of 51 patients per month. The average monthly recruitment in 2004 was 33 patients per month. If the summer rate continues, the study could be completed in less than two years. The study investigators continue to be concerned that patient cord blood and the two separate neonate heel sticks for bilirubin and glucose testing, which are needed to determine the study's primary outcome, are not being collected at delivery. While only 78.2% of all patients have all three samples collected, this is an improvement over the 75.4% reported in July.

## Progesterone Follow-up Study Proceeding Slowly

The follow-up of infants who were born while their mothers were on the original Progesterone trial continues to go slowly, with a third of the patients (about 100) still needing to complete the Ages and Stages Questionnaire (ASQ)

exam. The University of North Carolina is the first to recruit all four of their total patients, while three other centers are within one or two of their total (Wayne State-21 of 23, Brown-4 of 5, and Columbia-9 of 10). The University of Alabama, which recruited four times as many subjects as any other center, has enrolled 87 of their 116 patients. Thus far across all centers, only five patients have been declared lost to follow-up. It was announced at the July Steering Committee meeting that all fourteen nurse coordinators are on the protocol subcommittee and, thus, hold responsibility for the outcome of the study in addition to having authorship privileges.

## DSMC Plans Conference Calls for Reviews

The annual meeting for the DSMC will be held next Spring. However, the STTARS trial is recruiting so quickly that it was decided the DSMC needed to review an interim analysis report before then. Recruitment into the twins stratum is anticipated to finish in January and into the triplets stratum during next summer. Thus the trial will be reviewed by the Committee during a conference call on October 26. A separate call has been scheduled for December 8<sup>th</sup> to review and give feedback on the new TSH trial protocol.

## Notes of Interest



In case you are asked if the ingredients used to make the soft gel capsule itself for the CAPPS and Omega-3 trials are Kosher, the answer is "NO". While they are made of bovine (cow) gelatin imported from India to avoid Mad Cow Disease in Europe, they cannot be declared Kosher.

Proposals for analyte testing of fluids from the BEAM trial are due by the October Steering Committee Meeting.

## PEOPLE IN THE NEWS

**Above and Beyond...** The Society for Maternal-Fetal Medicine (SMFM) has posted on their web site a list of sub-specialists from around the United States who have volunteered to see patients displaced by Hurricane Katrina in their practice. Virtually all of the MFM investigators from the fourteen Network Centers have placed their name on this list. Dr. Susan Ramin, who hails from UT-Houston, wrote in passing that she was spending her weekend attending pregnant women who were housed in the convention center and that she had delivered 3 Katrina babies at Hermann Hospital.

As of late September, the following investigators from Network centers and affiliates had placed their names on the list: Drs. Andrews, Ramsey, Goepfert, Wenstrom (UAB), Drs. Mercer, Bailit, Catalano, etc. (Case), Dr. Dombrowski. (St. John/Wayne State), Drs. Silver, MacGregor, Sholl, Neerhof, Dinsmoor (Evanston /Northwestern), the MFM Division (Columbia), Dr. Moise (UNC), Drs. Landon, Iams, Samuels, Shellhaas, Durnwald, etc. (OSU), Dr. Berghella (Thomas Jefferson). In addition, at least one of the pediatric examiners for the Progesterone Follow-up study at Wake Forest has gone to the South to help the displaced who need medical care.

**Alexandre Braga** is the newest research assistant to join the BCC staff and has been assigned to the TSH trial. He is a native of Brazil but has lived in Canada and the USA for the last four years working as a research analyst and translator in the petroleum and petrochemical business. In Brazil, Alex analyzed census data and election statistics. He also collected and analyzed traffic statistics for the Metropolitan Urban Transport Department in Recife. His special interests include computers, electronic music production, films and tutoring math and English as a second language.

## Record Number of SMFM Abstracts Submitted

A total of twenty abstracts were submitted by Network investigators to the Society of Maternal-Fetal Medicine by the August 5<sup>th</sup> deadline, just beating the record of nineteen set last year. To date, of the 20 abstracts submitted to SMFM, one has been accepted for an oral plenary, 3 for oral concurrent sessions, and 14 as posters. Fourteen abstracts were submitted for the BEARS and C-Section studies alone. The authors of SMFM-accepted abstracts will present the results of their research at the October and December Steering Committee meetings.

Nineteen abstracts were proposed for SGI but were whittled down to ten by the protocol subcommittees prior to prioritizing by the Publications Committee. Completed SGI abstracts should be reviewed by the protocol subcommittee prior to forwarding them to the BCC statistician by October 18. Network investigators will be selected to review and comment on the abstracts. A conference call with the publications committee, reviewers, authors and statisticians is scheduled for October 21 to finalize and approve the abstracts before their submission to SGI on October 26.



### MUFMU CALENDAR

#### 2005 – 2006 Steering Committee Meetings

October 27-28, 2005      July 20-21, 2006  
 January 19-20, 2006      October 19-20, 2006  
 April 27-28, 2006

#### Professional Meetings

SMFM.....January 30-February 4, 2006, Miami, FL  
 SGI.....March 22-25, 2006, Toronto, Canada

#### Data Review Visit

University of Texas – Houston.....October 20-21, 2005

#### Publications Deadlines for SMFM/SGI 2006 Annual Meetings

SGI abstracts due to BCC.....October 18, 2005  
 Pubs call to approve abstracts.....October 21, 2005  
 SGI abstracts online deadline.....October 26, 11:59 PM CST  
 Deadline for SMFM 2004 manuscripts.....October 30, 2005  
 Deadline for SMFM 2006 manuscripts.....December 2005

## ... On the Light Side

