

ALPS Protocol Nearing Implementation

Following approval of the antenatal late preterm steroids protocol (ALPS) at the April Steering Committee meeting, BCC staff, and Drs. Cynthia Gyamfi, Ron Wapner and members of the subcommittee have ironed out many of the study details and have been working on the final protocol and data collection forms.



In this trial, women who present for imminent delivery between 34⁰ and 36⁵ weeks gestational age due to preterm labor, preterm PROM or because they have an indication for a planned delivery within 48 hours will be randomized to either a single course of corticosteroids or placebo. Women will be excluded if they have received prior steroids during the current pregnancy. There are two strata:

singleton pregnancies, requiring a sample size of 2400 women and twin pregnancies, requiring a sample size of 1400. The primary outcome is neonatal requirement for respiratory support after birth.

There is strong impetus for the trial. The rate of preterm birth has steadily increased in the United States over the past 10 years, driven in part by the rising rate of late preterm birth, defined as those births occurring between 34⁰ to 36⁶ weeks. Between 1992 and 2002, there was a 12% increase in births resulting from spontaneous preterm labor in this gestational time period; 21% of PPROM cases occurred in the late preterm period in 2002; and the rate of interventions in the late preterm group for medical indications increased by 12% over those ten years.

Late preterm infants experience a higher rate of readmission than their term counterparts and are more likely to suffer complications such as respiratory distress, kernicterus, feeding difficulties, and hypoglycemia. Late preterm infants also face increased

morbidity when compared with term infants, although data regarding outcomes in term versus late preterm infants are hard to obtain because of the lack of large studies.

Recently, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) held a workshop to address this emerging problem. One outcome of the workshop was the specific recommendation to study the effects of antenatal corticosteroids in the late preterm infant, particularly for multiple gestations. This research question is related to a recommendation made fourteen years ago by the NIH and the American College of Obstetricians (ACOG) that women who are at risk for preterm delivery prior to 34 weeks be given antenatal corticosteroids after research showed that the drug substantially reduces neonatal mortality, RDS and IVH. The current trial will determine whether or not corticosteroids also may be beneficial in late preterm infants.

Steering Committee Approves New 17P Study

Last April, the Steering Committee approved a new Network trial which will study whether 17 alpha hydroxyprogesterone caproate (17P), when used as adjunct therapy for women admitted for preterm labor, can decrease the incidence of preterm delivery and, therefore, improve neonatal outcome. The protocol investigators are Drs. Nicole Ruddock and Tony Wen from the University of Texas Medical Branch, Galveston, and Dr. Patrick Ramsey from the University of Alabama, Birmingham.

The proposed study will be a randomized, double-blind, placebo controlled clinical trial of weekly 17P or placebo administration to women who are admitted with preterm labor between 24⁰ and 31⁶ weeks gestation. Preterm labor will be defined as documented preterm contractions along with either cervical dilation and effacement, positive fetal fibronectin, or a shortened cervix ≤ 25 mm, measured

by sonographic exam between 24⁰ and 31⁶ weeks of gestation.

The proposed total sample size is 1,400 pregnant women and the primary outcome is the composite morbidity of the newborn.



Surgeon General Holds Conference on Preterm Birth

In December 2006, the Prematurity Research Expansion and Education for Mothers who Deliver Infants Early (PREEMIE) Act was passed by the U.S. Congress. This bill mandated a Surgeon General's conference to address the country's growing problem of preterm births. The conference, co-funded by the March of Dimes, was held in Bethesda, Maryland on June 16 – 17, 2008 and its scientific lead was NICHD.

The purpose was three-fold, to: increase awareness of preterm birth as a serious, common; and costly public health problem; review key findings and reports including the Institute of Medicine's (I.O.M.) report, *Preterm Birth, Consequences, and Prevention*; and establish an agenda and activities to identify and treat the causal and risk factors for preterm labor and delivery.

The closed session included the review of legislation, an overview of the I.O.M. Report, and presentations by experts in the field, including former P.I., Dr. Margaret Harper from Wake Forest University, about the state of the science and public health impacts. During the two-day session, workgroups including Biomedical Research (led by Drs. George Saade and Cathy Spong), Epidemiological Research, Psychosocial and Behavioral Considerations, Professional Education (*cont'd p. 3*)

Nurse Training for New Studies in July

Since the Network has two new ancillary studies ready to be implemented and a new research trial in development, a protocol training workshop has been scheduled for Wednesday, July 9, the day before the start of the July Steering Committee meeting. In addition to the ALPS trial, the training will familiarize the nurse coordinators regarding the ancillaries for the TSH and SCAN trials.

The *TSH ancillary*, proposed by Drs. Costantine, Smith and Boggess, was approved at the past April Steering Committee meeting and will study the impact of thyroid supplementation on pregnant women's emotional well-being during pregnancy. It is well known that serious thyroid disorders affect neuropsychiatric functioning and that there is a positive response when the condition is treated. However, the benefits of screening and treating pregnant women diagnosed with subclinical hypothyroidism have not been studied.

The research instrument being used for this ancillary study is the CES-D, a 20 item self-report questionnaire that was developed by the National Institute of Mental Health to measure depressive symptoms in the general population. The items that comprise the scale assess general psychological impairment, primarily depressive symptoms.

Patients will complete the test at the time of randomization (before taking any study drug), at a study visit between 32 and 35 weeks gestation and again at the 1-year infant follow-up, a year after they stop taking the study drug. The testing intervals should show whether or not treatment of subclinical hypothyroidism with levothyroxine affects the emotional well-being of both pregnant and post partum women. Scores from the questionnaire will not be analyzed until after the primary study has been completed.

The *SCAN ancillary (BAR-SCAN)*, proposed by Dr. Russ Miller of Columbia, will study the effect of the beta-2 adrenergic receptor (β_2AR) and variations in its genotype. Specifically, the objectives of this study are to determine whether:

- The beta 2 adrenergic receptor (β_2AR) and two specific variations in its genotype (Arg16 and Gln27) affect the incidence of a short cervix;
- These two genotypes influence the rate of preterm delivery and related pregnancy outcomes in women with a short cervix;
- Treatment with 17 α -hydroxyprogesterone caproate (17P) modifies the relationship between genotype and pregnancy outcome.

Blood will be collected from approximately 800 women who have been randomized to the SCAN trial because of their short cervix and from 400 women who were screened but found not eligible because their cervix was too long (40 millimeters or more - about normal for their gestational age). An attempt will be made for the women who are recruited into the normal cervix group to be similar in terms of race / ethnicity (African-American, Hispanic, Caucasian, Other) to the short cervix group. This will be achieved by instituting a quota system, by center, of the number of 'normal cervix' patients of given race / ethnicity that can be recruited on a monthly basis.

Surgeon General, cont'd
and Training, Public Communication and Outreach, and Quality of Care and Health Services convened and were charged with establishing an agenda with short, mid- and long-term goals. Other experts from the MFMU Network who also participated in the conference were Drs. Sean Blackwell, Jay Iams, and Brian Mercer.



Protocol Updates:

► The *APEX* study has been fully implemented since the beginning of this past April, although patient data collection began in March. As of June 25, there have been a total of 951 days of data collection between all of the 25 participating hospitals, resulting in 9,893 enrolled patients. Charts from 6,053 of these patients have been abstracted and entered into the data base. It appears that the number of eligible patients for this study per month across all centers is in line with the projected expectations of the study design (3,333 deliveries per month).

The data base is being carefully edited and audited. Thus far, the on-line web based data entry system is performing well. It is expected that data for the next trial conducted in the Network, ALPS, also will be entered on-line.

► The *TSH* trial continues to recruit well, and recruitment is anticipated to finish by the summer of 2009. As of June 30, 365 patients were enrolled in the S Stratum and 297 patients in the H Stratum. The one-year follow-up of infants has begun, with 12 Bayleys performed as of June 15. Training for the 24 month Bayley and the DAS (performed at the 36 month follow-up) is being planned for the end of 2008 or the beginning of 2009. Training for the ancillary study on the emotional well-being of patients will take place during the July 2008 Steering Committee meeting.



► The SCAN trial is recruiting more slowly than anticipated. The percentage of short cervixes noted on ultrasounds is running about as expected (9.4%); however, these nulliparous women who have had an ultrasound which identified a short cervix (< 30 mm) have not consented to participate in the trial as we anticipated, even though progesterone may prove to prevent a preterm delivery for them. Ultrasounds have been performed on 5,156 women as of July 2, 2008, with 403 women found eligible. Of these, only 190 have given consent to participate in the Network trial and 156 have been randomized. Columbia has screened the most patients (1,232) with 19 eventually randomized. Brown has the highest percentage of

patients who were screened eligible and consequently randomized (5 out of 6 patients).

Given the high ratio of screened patients to randomized patients at some centers, NICHD recently proposed that capitation be re-structured to reduce the high costs of screening and at the same time yield more randomized patients. The suggested strategy for centers is to make sure that patients are pre-screened for possible exclusions before having the screening ultrasound, and that the patients are better informed about the rationale for the trial, the reasons they are being screened, and expectations if they are found to have a short cervix, all of which are outlined in the informed consent forms signed by patients.

Winner of the "Cross Number" Puzzle

Todd Rosen, MD, from Columbia University was the first to solve the puzzle presented in the March issue of the *Networker*. The puzzle was a palindrome (a number that reads the same forwards and backwards) and was about when certain presidents were first elected. Congratulations, Todd!!

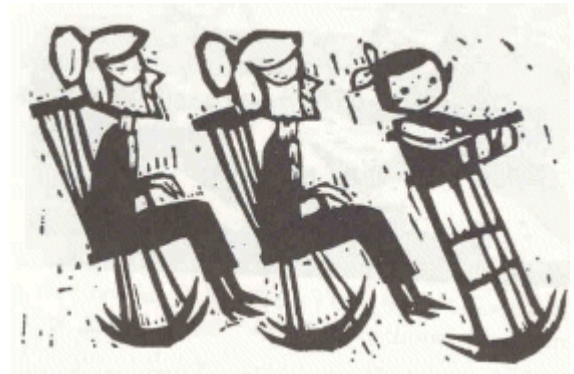
Solve the following puzzle and be the first to submit the solution to Lucy_L@bsc.gwu.edu to win recognition in the next newsletter.

AN AGE PROBLEM

Lottie and Linnette Hill are both 90 years old. Mary Jones, on the other hand, is half again as old as she was when she was half again as old as she was when she lacked five years of being half as old as she is now.

How old is Mary?

NOTE: "Half again" is an old way of saying "one-and-one-half times." Thus, if John is 20 and Jim is "half again as old as John," then Jim is 30.



MFMU CALENDAR

Network Meeting dates for 2008

October 23 – 24

Network Meeting dates for 2009

January 8 – 9

April 23 – 24

July 9 – 10

October 22 – 23

2009 SMFM Abstract Deadlines

Email to MFMUPROP@bsc.gwu.edu: August 1, 2008
 Publications Committee Conference Call: August 5, 2008
 Submission to SMFM: August 8, 2008