

Implementation of APEX Revised

The pilot study for the new APEX protocol successfully accomplished its goal – namely, to identify the difficulties and the pitfalls of the procedures required to collect the data needed to determine the primary outcomes and process measures of the protocol. Twenty-two hospitals participated in collecting data on seven randomly assigned days between November 26 and December 9.

One of the first issues noted was that the patient medical charts were not immediately completed and available, so that the data was could not be abstracted in time to key into the computer before the December 29th deadline. The nurse coordinators asked the subcommittee to re-assess the timeline and push back the date for data entry. This change, however, would require delaying the start of the study slated for March 1, since there would be less time to assess the pilot data and re-work any data forms for the main study. In addition, it was realized that delaying the start would have potentially adverse financial and staffing implications for the centers.

After discussion, the subcommittee revised the timeline so that January 31, 2008, is the new deadline for keying all of the pilot data. April 1 is the start of the main study, which still allows two months for analysis of the pilot data and revision of the data forms, the internet data entry system and the manual of operations. To limit the financial burden, patient data will be collected retrospectively for the month of March. Thus, capitation will be provided for patient data collected in March. Centers will be provided with their randomly-assigned data collection days prior to March 1.

The nurse coordinators will attend a meeting with the protocol chairs and the BCC on January 9, during which the background, objectives and inclusion/exclusion criteria will be reviewed. A descriptive summary of the pilot data will be presented. The coordinators have been asked to submit their comments for consideration prior to the meeting so that these will also be summarized. Problems encountered by the nurses when completing the forms will also be discussed and their suggestions will be solicited regarding the flow and order of the questions on the forms.

Three hospitals still need to obtain IRB approval for the protocol. It is expected that this will be accomplished so that they can collect pilot data for two weeks prior to March 1.

Two Concepts Approved for Protocol Development

The Steering Committee members approved moving two concepts to the protocol stage at their meeting last October. The first is a randomized, double-blind placebo-controlled trial to see if administering antenatal corticosteroids at 34 to 36 weeks 6 days will decrease the need for admission to a specialized unit (NICU/Step-down/Transitional nursery) for respiratory support. Dr. Gyamfi from Columbia University successfully presented the miniprotocol. There would be 2000 women in each arm.

The second approved concept is also a randomized, double-blind placebo-controlled trial using 17-Alpha Hydroxyprogesterone caproate (17P) as an adjunct therapy for preterm labor. The hypothesis is that acute preterm labor followed by maintenance 17P decreases neonatal mortality and morbidity in women admitted for preterm labor. Dr. Ruddock from UT Medical Branch in Galveston successfully presented the miniprotocol.

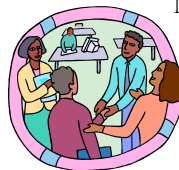
GDM Trial Finishes Recruitment

After nearly five years, the final patient was randomized into the Network's trial of mild gestational diabetes mellitus on November 7. A total of 1889 patients were enrolled into Groups I and II. Since the last delivery and follow-up will take place this Spring, there will be time to analyze the data and prepare an abstract for submission to SMFM's annual meeting in 2009.

It is important that the remaining delivery samples are collected per the protocol. Except for the calipers, any left over study supplies may be donated to diabetes programs at Network center hospitals. The calipers should be stored in the MFMU

Network center office for future studies.

Many thanks to all of you who persevered to identify, screen and enroll eligible patients and then follow them through delivery – it was not an “easy” trial and your efforts to overcome obstacles are much appreciated!



Congratulations!

Revisions Made to TSH Trial Protocol

As planned in the TSH protocol, the distribution of TSH and free-T4 values were assessed early last October, at which point about 17,000 women had been screened. At that time, the 97.5th percentile for TSH was considerably higher than the chosen threshold of 3 mU/L. Of the 203 patients enrolled in the subclinical hypothyroidism (S) stratum, only 65 were above the actual 97.5th percentile based on the cohort of patients screened to date for the trial. The 3 mU/L level that had been chosen for the protocol was based on the best available data before the trial began.

As a result of this assessment, the subcommittee recommended to the Steering Committee that the TSH threshold for screening be changed from 3 mU/L to 4 mU/L. The subcommittee did not recommend any changes to the free-T4 levels. The Steering Committee approved the recommendations, which required the sample size for the S stratum to increase to 670 from the original number of 500. A

revised protocol was distributed to the centers in mid-November and should have been submitted to IRBs for approval. The DSMC also approved this change.

This change in eligibility for the S stratum has resulted in a drop off in the number of eligible patients. However, the initial estimated number of 120,000 women required for screening is not expected to increase as a result of the larger sample size. The current numbers are in line with what was originally expected so recruitment remains on target.

Infants born to the first mothers enrolled in the TSH trial will be reaching their first birthday shortly after the beginning of the new year. A training to familiarize the follow-up examiners with the Bayley III exam and MFMU Network procedures was held October 15. A conference call with the follow-up coordinators has been scheduled for mid-January. The follow-up manual of operations, the two data forms (TH14 – Follow-up Medical History Form and TH14A - Family Status Form) and other procedures that will be completed at the one year exam will be reviewed and discussed.

Publications and Presentations Plentiful in 2007

The MFMU Network continued to be very productive in 2007, with fourteen major publications, including two in the *New England Journal of Medicine*. Three additional papers have been accepted for publication. Abstracts presenting results from two studies (BEAM and Omruga-3) were chosen for the opening plenary session at the 2008 annual meeting of the Society for Maternal-Fetal Medicine (SMFM). These two abstracts were ranked as the first and third of over 1000 abstracts submitted. In addition, another one of the SMFM abstracts was chosen for an oral. In all, there were 12 abstracts chosen for SMFM and 4 abstracts chosen for the 2008 Society for Gynecological Investigation (SGI) meeting.

Following Network policy, the primary authors of the SMFM abstracts will be presenting their analyses at the January 2008 Steering Committee meeting to receive

suggestions regarding manuscript and presentation preparation prior to presentation at the meeting. In addition, if the manuscript is intended for publication in the SMFM special issue of the *American Journal of Obstetrics and Gynecology*, the primary author with his/her BCC statistician should be preparing a draft manuscript for review before the abstract is presented at the meeting. Following review by the Protocol subcommittee and authors, the manuscript is reviewed by 2 primary reviewers, the Publications Committee, the BCC (for statistical clearance) and finally the NICHD. To allow time for these steps, manuscripts were due to the Publications Committee by December 15th if they were intended for the special issue devoted to the SMFM.

Following is the list of 2007 publications.

- Grobman WA, Gilbert S, Landon MB, Spong CY, Leveno KJ, Rouse DJ, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, O'Sullivan MJ, Sibai BM, Langer O, Thorp JM, Ramin SM, Mercer BM. Outcomes of induction of labor after one prior cesarean. *American Journal of Obstetrics and Gynecology*, 109:262-9, 2007.
- Alexander JM, Leveno KJ, Rouse DJ, Landon MB, Gilbert S, Spong CY, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, O'Sullivan MJ, Sibai BM, Langer O, Gabbe SG; National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU). Comparison of maternal and infant outcomes from primary cesarean delivery during the second compared with first stage of labor. *American Journal of Obstetrics and Gynecology*, 109:917-921, 2007.

(2007 Publications, cont'd)

- Berghella V, Owen J, MacPherson C, Yost N, Swain M, Dildy GA, Miodovnik M, Langer O, Sibai B; National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU). Natural history of cervical funneling in women at high risk for spontaneous preterm birth. *American Journal of Obstetrics and Gynecology*, 109:863-9, 2007.
- Grobman WA, Lai Y, Landon MB, Spong CY, Leveno KJ, Rouse DJ, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, O'Sullivan MJ, Sibai BM, Langer O, Thorp JM, Ramin SM, Mercer BM for the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU). Development of a nomogram for prediction of vaginal birth after cesarean delivery. *American Journal of Obstetrics and Gynecology*, 109:806-12, 2007.
- Hendler I, Andrews WW, Carey CJ, Klebanoff MA, Noble WD, Sibai BM, Hillier SL, Dudley D, Ernest JM, Leveno KL, Wapner R, Iams J, Varner M, Moawad A, Miodovnik M, O' Sullivan MJ and Van Dorsten PJ. The relationship between resolution of asymptomatic bacterial vaginosis and spontaneous preterm birth in fetal fibronectin-positive women. *American Journal of Obstetrics and Gynecology*, 197, 488-490, 2007.
- Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, Varner M, Malone F, Iams JD, Mercer BM, Thorp J, Sorokin Y, Carpenter M, Lo J, Ramin S, Harper M, Anderson G for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *New England Journal of Medicine*, 357:454-61, 2007.
- Sawady J, Mercer B, Wapner RJ, Zhao Y, Sorokin Y, Johnson F, Dudley DJ, Spong CY, Peaceman AM, Leveno KJ, Harper M, Caritis SN, Miodovnik M, Thorp JM, Ramin S, Carpenter MW, Rouse DJ for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.. Beneficial effects of antenatal repeated steroids study: impact of repeated doses of antenatal corticosteroids on placental growth and histologic findings. *American Journal of Obstetrics and Gynecology*, 197: 281-288, 2007.
- Wapner RJ, Sorokin Y, Mele L, Johnson F, Dudley DJ, Spong CY, Peaceman A, Leveno KJ, Malone F, Caritis S, Mercer B, Harper M, Rouse DJ, Thorp JM, Ramin S, Carpenter MW, Gabbe SG for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Long term outcomes of a randomized trial of repeat antenatal corticosteroids. *New England Journal of Medicine*, 357: 1190-1198, 2007.
- Louis J, Landon MB, Gersnoviez RJ, Leveno KJ, Spong CY, Hauth JC, Moawad AH, Varner MW, Caritis SN, Harper M, Wapner RJ, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai BM, Langer O, Thorp JM, Ramin SM, Mercer BM for the NICHD Maternal-Fetal Medicine Units Network. The MFMU Cesarean Registry: Perioperative morbidity among HIV infected women undergoing cesarean delivery. *Obstetrics and Gynecology*. 110:385-390, 2007.
- Landon MB, Thom E, Spong CY, Carpenter M, Mele L, Johnson F, Tillinghast J, Anderson G for the NICHD Maternal-Fetal Medicine Units Network. The NICHD MFMU-Network randomized clinical trial in progress: Standard therapy versus no therapy for mild gestational diabetes mellitus. *Diabetes Care*, 30: S194-S199, 2007.
- Northen AT, Norman GS, Anderson K, Moseley L, DiVito M, Cotroneo M, Swain M, Bousleiman S, Johnson F, Dorman K, Milluzzi C, Tillinghast J, Kerr M, Mallett G, Thom E, Pagliaro S, Anderson G for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Follow-up of children exposed in-utero to 17-alpha hydroxyprogesterone caproate versus placebo. *Obstetrics and Gynecology*, 110: 865-872, 2007.
- Varner MW, Thom E, Spong CY, Landon MB, Leveno KJ, Rouse DJ, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin RJ, Miodovnik M, Carpenter M, Peaceman A, O'Sullivan MJ, Sibai BM, Langer O, Thorp JM, Ramin SM, Mercer BM for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Trial of labor after one previous cesarean delivery for multifetal gestation. *Obstetrics & Gynecology*, 110:814-819, 2007.

