



The MFMU Networker

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Press Recognizes Import of Progesterone Trial

The day after Dr. Paul Meis presented the results of the Progesterone trial at the plenary session of the annual meeting of the SMFM, the findings were printed in the *New York Times*, the *San Francisco Chronicle*, the *Washington Post* and reported on CNN. This major, groundbreaking trial showed that the hormone, 17 alpha hydroxyprogesterone (17P), reduced preterm birth by 34% of women who were classified as high risk because of a previous preterm delivery. Treatment was equally effective in African American and non-African American subjects, and in the prevention of spontaneous and indicated preterm births. In this trial, pregnant women received weekly injections beginning at 16 to 20 weeks of gestation which were continued until 36 weeks gestation.

Dr. Meis, PI for the trial, continues to be interviewed and publications in the lay press continue to report the results of this trial. A pharmaceutical firm is already making the hormone available to doctors.



Data and Safety Monitoring Committee. The issue was thoroughly discussed both at the Subcommittee and Steering Committee levels. As a result, the patient management section in the FOX protocol has been changed to include a broadened definition of "ominous" fetal heart rate. The informed consent form also was changed to indicate to the patient that labors monitored with electronic fetal heart rate monitoring alone or combined with fetal pulse oximetry have both been occasionally associated with adverse pregnancy outcome including stillbirth.

Each Network PI also has taken the responsibility to ensure that each clinician at their clinical center been educated regarding the clarifications and changes to the management protocol. The FDA strongly supports the position taken by the NICHD in reaction to these findings and has encouraged the Network to finish the trial.

CAPPS Taking Off

Despite numerous setbacks, the Combined Antioxidants and Preeclampsia Prediction Studies (CAPPS) should be starting in April. The main obstacle occurred in January when the FDA required the NICHD to file an Investigational New Drug (IND) for the trial, even though vitamins are exempt from FDA regulation. The reason given was that vitamins are being used to alter a condition (preeclampsia) in a high risk group (pregnant women).

The IND requires more technical data, such as chemistry, manufacturing, control, pharmacology and toxicology, than the nutritional manufacturer that had been selected could provide. Thus a new manufacturer needed to be found and specifications and production standardized before the IND could be written and submitted to the FDA. Eminent Services, which has supplied drug packaging, stability testing and surveillance, among other services for the Network, was able to find a manufacturer (Strides, Inc.) and produce the IDE which was submitted March 14, less than two months after the crisis!

Meanwhile, protocol training was held February 19, for the coordinators and research nurses. Drs. Les Myatt and Menachem Miodovnik were on hand to help train and answer questions. Coordinator, Peggy Cotroneo brought Rob McCorkle, lab technician at Magee-Womens, to demonstrate how to cut the blocks from actual placentas. Rob offered a hands-on opportunity to do some cutting, which most of the attendees took advantage of trying.

The protocols, one for the RCT portion of the study, which studies the effect of vitamins C and E on preeclampsia, and one for the observation portion of the study which studies factors that might predict preeclampsia, were modified after the training. The manual of operations, which serves for both studies, and the data forms have been finalized. Most centers have submitted their materials for IRB consent and have begun working on certifying study personnel. The study drugs will be prepared and distributed by the end of March. Since decisions remain to be made for the prediction study concerning which fluids analyses will be done and how much blood and urine will need to be collected from patients, the RCT part of the study will begin first.



Results of Factor V Leiden Study Reported

Dr. Donna Dizon-Townson, presented the results of the Factor V Leiden study, for which she was PI, at the annual meeting of SMFM last month. Contrary to retrospective analyses, the study found that Factor V Leiden (FVL) carriers do not have an increased risk for adverse pregnancy outcomes, including pregnancy-related venous thromboembolic events (VTE).

A total of 5,188 pregnant women, less than 14 weeks gestation, underwent FVL DNA testing of which 134 were found to be carriers for FVL, all of whom were heterozygous. There were four VTE events and all occurred in women who did not carry the mutation.

Dr. Dizon-Townson's poster presentation won first place at SMFM. The results are significant since universal prenatal screening for FVL and prophylactic treatment of heterozygous carriers, without a prior VTE, are no longer indicated.

Tyco and FDA Impact FOX Trial

Early in February, Tyco Healthcare, the manufacturer of the N400 oximeter used in the FOX trial, sent a letter to clinicians clarifying existing instructions for use of the N400 and introducing additional changes to the clinical management protocol. The letter was issued after several poor neonatal outcomes with the N400 were reported to the FDA.

Action has been taken by the NICHD and the BCC, including a meeting with the FDA which holds the Investigational Device Exemption (IDE) for the trial and a conference call with the chair of the

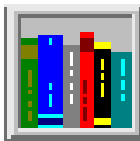
New Network Publication Process Defined

In order to expedite and facilitate the publication of manuscripts reporting the results of the Network's research, the Publications Committee has developed a 'Manuscript Sign-off Form'. The form lists the specific tasks with deadlines that must be taken by the author, the protocol subcommittee, the reviewers, NICHD, the BCC, and the Publications Committee to process the manuscript all the way through to submission to a professional journal.

The form is available on the MFMU web site and should be attached to the manuscript and updated as it proceeds through each phase via e-mail. Susan Pagliaro, Network Coordinator, would appreciate any suggestions on how to make this form, which is in a 'pilot phase', more user-friendly.

The Publications Committee also has begun the task of cleaning up the backlog of partially completed analyses, in addition to completed analyses which have been presented at professional meetings but not yet published, to determine which projects will be pursued. Individual authors are being contacted to determine if they intend to pursue their research and/or write a manuscript on the results. In addition, the Analysis Status spreadsheet, which lists all Network analyses and the status of resulting publications and is also posted on the web site, will be revised to specify the date when it moves from one phase (eg, subcommittee only) to the next.

Investigators who are presenting abstracts at professional societies this year - SMFM (14), SGI (4), ACOG (1) - this year already have been asked if they plan to write a manuscript and have been given a deadline for starting the process. This effort is being initiated so that the findings of the Network's research reaches members of the profession in a timely, relevant fashion.



Centers Issued Progress Reports

In order to give each Network Center an indication of its standing compared to other centers and also perhaps identify problem areas, Dr. Cathy Spong, Program Scientist for the MFMU Network, has released a mid-competition cycle progress report to Network PIs. The ranking of centers is based on patient recruitment to Network trials between October 2001 and the end of January 2003. Other ranking factors include the number of protocol violations, the percentage of successful patient follow-up, the percentage of patients with overdue forms, and number of edits and audits per 1000 fields keyed. Different variables, such as study and dates covered, are used for each factor in the computation.

Dr. Spong has emphasized that the progress report will not go into each center's file. It is meant to give centers feedback on how they compare with others in the Network. She sees this an opportunity to assess how centers might be helped to overcome specific difficulties.

Bears Update

Investigators from the Steroids trials being conducted in the USA and Canada held a joint meeting at the annual meeting of SMFM in February to compare progress. The PIs from both trials, Drs. Ron Wapner and Kellie Murphy, expressed pleasure over the increase in recruitment seen in each other's studies. They expressed hope that several new studies that have been published recently showing corticosteroids do not adversely affect birth weight and head circumference will help recruitment even more. In addition, talk among physicians about potential risks seem to have diminished. Regardless of how long the trial lasts, the PIs are hopeful that an adequate number of patients have been enrolled in the trials to finally determine whether, in fact, any safety issues do exist.

Network's DSMC and Advisory Board Meet in March

The NICHD and BCC were busy in March preparing for meetings with the MFMU's new Advisory Board and the Data Safety and Monitoring Committee, both of which now include new ad hoc members for the CAPPs and MOMS trials.

The Advisory Board, which had not been convened in person since 2000, was briefed on the history of the Network and current projects at its March 6 meeting. The Advisory Board is charged with evaluating and providing feedback on proposed new studies in the Network and even suggesting research ideas and priorities. Some of its members are no strangers to the Network, having previously served on the Steering Committee, particularly Drs. Baha Sibai, Mary Jo O'Sullivan and Don Dudley. The members were asked specifically to provide feedback on the CAPPs trial and the next study in the pipeline, the Omega-3 trial.

The DMSC, which met on March 20, reviewed the status of the Network's current trials: BEARS, BEAM, GDM and FOX, as well as the Fetal Surgery Unit's Management of Myelomeningocele Study. Comprehensive reports were prepared and presented by the BCC.

C-Section Countdown

No new forms for the c-section study can be keyed after the April 3 transmission of data. Only patients who have the required forms entered will be capitated. Therefore, it has been recommended that Centers concentrate on getting complete records for patients who were enrolled earlier. If centers are not allowed to respond to edits and audits as a result of their IRB's position on the Privacy Rule, they should stop entering new data forms and focus on fixing data on existing forms.

Data collected during the first two years of the study finally will be locked at the end of March.

HIPAA is Happening

In preparation for the new privacy regulations under HIPAA, which take effect on April 14, Lora Kutkat from the Office of Science Policy in the Office of the Director of NIH was asked to present an overview explaining the Rule and its impact on medical research at the February Steering Committee meeting. Her presentation generated a good deal of interest and questions, since many of the Network staff already are receiving directives from the IRB or Privacy Officer at their center.

It was apparent that officials at individual centers are handling the issues in somewhat different ways. Therefore, the Network has decided that each center will need to follow the instructions concerning research and privacy as issued by their individual IRB. These directives affect current protocols in addition to new ones such as CAPPs.

NIH is coordinating educational materials concerning the Privacy Rule for researchers. Lora Kutkat welcomes questions and can be reached at 301-594-2464 or kutkatl@od.nih.gov.

Two Centers in NC Host Site Visits

In late January, BCC PI, Elizabeth Thom, along with Steve Weiner, Maureen Hoover and Lucy Leuchtenburg, made a site visit to Wake Forest University in Winston-Salem and UNC in Chapel Hill. As always, the BCC team found it extremely valuable to meet with staff and tour the



Wake Forest Staff: Linda Steele, Missy Swain, Kristi Lanier, Cheryl Moorefield

facilities. Both centers have an additional recruiting site so it was informative to see how the arrangements and communication between the sites had been established.

Patient medical charts were reviewed and compared with study data forms by the team that also visited the pharmacies and examined the drug logs. Each visit concluded with a wrap up session that included an exchange of findings, suggestions and recommendations between the

center and the BCC.

BCC staff appreciated the time-consuming preparations made by each center, and especially appreciated the delicious dinners that also provided the opportunity to visit with staff on an informal basis. Site visits by the BCC to other MFMU Network centers are being contemplated.



UNC-Chapel Hill Staff: Karen Dorman, Dr. John Thorp, Jeanne Mitchell, Janice Bernhardt



Network Software News

Data Forms Audit: The recent Data Forms Audit, the first since the new VFP data entry system was implemented, uncovered an increase in data entry errors for the FOX trial. Most of the errors are attributed to not keying

exactly what has been entered on the data form when the 'smart skip' function is on and keying errors on the 'log-like' forms (MK04 and MK05). Use of the double data entry, which should help catch some of these errors, is encouraged. A double data entry reporting module has been added to the software which allows monitoring of its use. The BCC's Julia Zachary sent all coordinators a memo concerning these issues in mid-March.

Study Forms Revisions: Several forms from the GDM trial and the FOX MK05 screen have been updated. The software updates will be sent to each center to be installed after the April 2 but before the April 9 transmission.

Staff Update: We wish Alysia Jones all the best on her recent marriage to Elberkus Jongerling, a lepidopterist from Holland. Alysia has worked on the Network's software program since its inception in 1987, and was responsible, along with Julia Zachary, for much of its development over the years. She also led most of the software training sessions. Her husband has already named a butterfly after her. They honeymooned in Costa Rica where he has studied the species, before returning to Europe.

May Boonyobhas, who has supported the software programmers for several years, in addition to working with centers on the BEARS and BEAM ultrasounds, will be graduating with a computer degree later this year. She will continue training as a programmer at the BCC, assisting Natasha Khanna with some of the data transmission.



Dr. Steve Gabbe Announces Resignation

To the dismay of the Network, Dr. Gabbe announced his resignation as Chair of the MFMU Network at the February Steering Committee meeting. Citing other demands of his career, especially his duties as Dean of the College of Medicine at Vanderbilt, Dr. Gabbe felt he could not continue to provide the leadership needed to run the Network. Chair of the Network since 2001, his departure was immediate. Potential candidates currently are being considered for the position.

Iams Installed as New SMFM President

Dr. Jay Iams, a MFMU Network PI since 1992 and internationally respected expert in high-risk obstetrics at The Ohio State University Medical Center, was installed as president of the Society for Maternal-Fetal Medicine at the Society's annual meeting last month in San Francisco. The society has almost 3000 members from around the world and works to promote prevention and treatment of high-risk pregnancies. He has served on the Society's Board of Directors since 1998, and was elected vice president and president-elect in 2002.

Dr. Iams graduated from the University of Wisconsin with a degree in political science before obtaining his medical degree from Wisconsin. He did his residency in pediatrics in Phoenix, Arizona prior to an additional residency in OB/GYN and then a MFM fellowship at Ohio State. Besides being professor of medicine at OSU, he has also served as director of the division of MFM and is currently the Vice-Chairman of the Department of OB/GYN. He also holds the Frederick P. Zuspan Endowed Chair in OB/GYN at OSU. He has been listed in every edition of *Best Doctors in America* since 1993. He is a fellow of the American Gynecological and Obstetrics Society and a member of the Board for the American Board of Obstetrics and Gynecology, MFM Division. He is the Associate Editor of the *American Journal of Obstetrics and Gynecology*. He is also an editorial consultant to many other journals, including the *New England Journal of Medicine*.

Dr. Iams was the PI for the Home Uterine Activity Monitoring study conducted by the Network. He has also served on a number of Network Subcommittees. In between his medical service and research, volunteer work, honors and teaching, he and his wife Pat have raised five children.

Interim Grants Administrator Named

Mary Ellen Colvin has been selected to take over as the MFMU Grants administrator. She's no stranger to the Network as she was its grants administrator from 1991 - 1999. After she left the NICHD MFMU Network, she became responsible for a portfolio of grants processed through the NICHD's Center for Populations Research (CPR). As a grants administrator, she was responsible for more than 300 grants. Currently she serves as the acting Team Leader for the team of grants specialists responsible for the CPR.

Mary Ellen enjoys traveling with her husband and is looking forward to retirement next year after 38 years of government service. She welcomes questions from the Network and can be reached at (301) 496-1304. Her email is MC113B@NIH.GOV.

Web Site Modification

Please note that the *MFMU Networker* has been moved to the Business Section of the MFMU web site. It was decided that, since most of the *Networker* concerns the day-to-day operations of the Network, it was more appropriate for members and associates of the Network than the general public.

Steering Committee Agenda Format Changed

The Steering Committee has agreed to institute a generic meeting agenda in an effort to eliminate overlapping subcommittee meetings. Investigators have been asked to make their travel arrangements so they can participate in the full meeting. The schedule is as follows:

Day 1:	8am - 11am	Nurse coordinator meeting
	11am - 12pm	Subcommittee meeting
	12pm - 5pm	Steering committee meeting
	5pm - 8pm	Subcommittee meetings
Day 2:	7am - 8am	PI meeting
	8am - 12pm	Steering committee meeting
	12pm on,	Additional subcommittee mtgs as needed

Investigators are requested to notify NICHD well in advance of the meeting if a subcommittee meeting needs to be scheduled. In addition, conference calls should not be held within 5 working days of the Steering Committee meeting. In order to allow ample opportunity for view, written materials should be emailed to Susan Pagliaro for distribution two weeks prior to the meeting. Presentations should be brought to the meeting either on diskette, CD-ROM or USB port. They should be loaded on the computer prior to the beginning of the meeting or during a break. Plugging in personal computers may cause problems for the A/V system, resulting in no visuals.

Investigators have also been reminded that ancillary concept proposals must be approved by the appropriate subcommittee before being presented to the Steering Committee meeting.

MFMU CALENDAR



Steering Committee Meetings

May 5-6, 2003
 July 14-15, 2003
 October 23-24, 2003

Dates for 2004 Steering Committee Meetings will be finalized soon.

Important Protocol Dates

- Final data forms entered for C/S - April 3, 2003 transmission
- BEAM/BEARS Ultrasound Review - April 24-25, Washington, DC

SGI Annual Meeting

March 27-30, 2003, Washington, DC

ACOG Annual Meeting

April 28-30, 2003, New Orleans, LA

Society for Clinical Trials Annual Mtg

July 20-24, 2003, London, England

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