



# The MFMU Networker

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## Multiple Dose Steroids Trial Update

Contributed by Ron Wapner, MD

The NIH Consensus Conference, held last August, strongly supported a randomized clinical trial comparing single versus repetitive doses of antenatal glucocorticoid therapy. The Consensus Panel felt that there was some evidence to support possible efficacy for multiple doses compared with single doses. The group, however, also felt that the information about the potential risks needed further evaluation.

Presentations to the Consensus Panel included a meta-analysis by Kellie Murphy which used both published reports and abstract data and demonstrated a significant decrease in RDS and no alternations in fetal growth. Other presentations also showed a reduction in RDS and a decrease in the frequency of patent ductus. The Panel concluded that, because of the uncertainty about the efficacy and the safety of multiple dose corticosteroids, including a rescue dose, they should only be used in randomized trials. The intent was to allow additional information to be obtained. However, this has been misinterpreted by many physicians to mean that the Consensus Panel suggested a moratorium on multiple dose use. *This was not the case.* The Consensus Panel was very supportive of the Network's randomized trial as well as three other trials in Canada, Britain and Australia.

To assist in the recruitment for this study, the steroid subcommittee has been diligently working on information pamphlets for patients and physicians. These include the most recent information on both the efficacy of repetitive versus single doses as well as an appropriate perspective on the potential hazards. The pamphlets will be finalized at the subcommittee meeting to be held with the next Steering Committee meeting and then disseminated to all centers.

Almost one-third of patients receiving repetitive dose steroids are twin gestations. The initial corticosteroid protocol excluded twins, in part because of a potential conflict with the BEAM Study. However, the BEAM subcommittee has recently agreed to allow multiple gestations to be utilized for the steroid trial. This change has been approved by the subcommittee and all centers have been notified. This should provide a major boost in patient recruitment. It should also be noted that, unlike singleton gestations, a specific cervical change is not required for enrollment of twin gestations.

Finally, additional information has become available about the efficacy and risks of repetitive steroids. The NICHD NICU Network has recently prepared an abstract for submission to SPR that has evaluated over 5,000 low birth weight infants. This study demonstrated a reduction in the risk of death or severe neurodevelopment impairment as determined by a Bailey MDI or PDI <70, CP, deafness or blindness. There was also no discernable effect on growth or cerebral palsy in the group receiving repetitive doses. The repetitive dose group did have an increased risk of BPD. While these studies are retrospective, they demonstrate the continued importance of this trial.

## MFMU Abstract Chosen for 7<sup>th</sup> Straight SMFM Plenary

For the 7<sup>th</sup> straight year, a MFMU Network abstract has been selected to be one of eight presentations at the main plenary session of the annual meeting of

SMFM. The honor this year falls to former PI, Dr. Mitch Dombrowski from Wayne State, who will be presenting the results of the



*Randomized*

*trial of inhaled beclomethasone vs theophylline for asthma during pregnancy.* Over the years, a total of eleven abstracts have been chosen for the plenary session. Twelve of the other Network's 15 presentations and posters were also accepted (see the list in the September issue of the *Networker*). Since the beginning of the Network through year 2000, there have been 115 presentations reporting the results of the Network's research.

## MFMU Network Applications Reviewed

A special emphasis panel of peer reviewers, convened by NICHD, met November 28-29 to consider applications for the next five-year cycle of the MFMU Network. Thirty-five applications were reviewed and the scores have been sent to the (*cont'd page 3*)

## Record Set for Number of Journal Publications in One Year

Eleven publications reporting results of MFMU Network research were issued by major medical journals during 2000, three more than last year! Included in these was the original article on the BVTV trial results in the *New England Journal of Medicine*. The list of this year's publications is below.

About 150 analyses have been done on the 18 studies and ancillaries completed since the NICHD MFMU Network was started in 1986. Of these, more than 60 have been accepted or published by medical journals. And of these, more than two thirds (about 40 articles) have been published in just the past 5 years! The Preterm Prediction study (singletons and twins) has provided the most fruit, with 23 papers accepted or published. The ODNs and High Risk Aspirin studies are second, each with 6 papers currently published. Numerous other analyses for other completed studies, such as the BV/TV trial and Asthma studies, are currently being worked on. The complete list of publications and status of each analysis can be found on the MFMU Business web site.

Goldenberg RL, Andrews WW, Guerrant RL, Newman M, Mercer B, Iams J, Meis P, Moawad A, Das A, Van Dorsten P, Caritis S, Thurnau G, Bottoms S, Miodovnik M, McNellis D, Roberts JM for the NICHD Maternal Fetal Medicine Units Network. ***The Preterm Prediction study: cervical lactoferrin concentrations, other markers of lower genital tract infection and preterm birth.*** *Am J Obstet Gynecol*, 182(3):631-635, 2000.

Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, Menard MK, Caritis SN, Thurnau GR, Dombrowski MP, Das A, Roberts JM, McNellis D, and the NICHD Maternal Fetal Medicine Units Network. ***Is socioeconomic status a risk factor for bacterial vaginosis in black or in white women?*** *Am J Perinatology*, 17:41-45, 2000.

Goldenberg RL, Iams JD, Das A, Mercer BM, Meis PJ, Moawad AH, Miodovnik M, Van Dorsten JP, Caritis S, Thurnau G, Dombrowski MP, Roberts JM, McNellis D and the NICHD Maternal Fetal Medicine Units Network. ***Sequential cervical length and fetal fibronectin testing for the prediction of spontaneous preterm birth.*** *Am J Obstet Gynecol*, 182(3): 636-643, 2000.

Goldenberg RL, Andrews WW, Mercer B, Moawad A, Meis P, Iams JD, Das A, Caritis S, Roberts JM, Miodovnik M, Menard MK, Thurnau G, Dombrowski MP, McNellis D for the NICHD Maternal Fetal Medicine Units Network. ***The Preterm Prediction Study: granulocyte colony stimulating factor and spontaneous preterm birth.*** *Am J Obstet Gynecol*, 182(3): 625-630, 2000.

Goldenberg RL, Das A. ***Fetal fibronectin and bacterial vaginosis in smokers and non-smokers.*** *Am J Obstet Gynecol*, 182(1):164-166, 2000.

Sibai BM, Caritis S, Hauth J, Lindheimer M, VanDorsten, MacPherson C, Klebanoff M, Landon M, Miodovnik M, Paul R, Meis P, Dombrowski M, Thurnau G, Roberts J and McNellis D for the NICHD Maternal Fetal Medicine Units Network. ***Risk of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus.*** *Am J Obstet Gynecol*, 182(2): 364-370, 2000.

Hogg B, Hauth JC, Meis PJ, Roberts JM, Meikle S. ***Reply to: What is the meaning of authorship?*** *Am J Obstet Gynecol*, 183(3):775, 2000.

Alexander JM, Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Das AF, Meis PJ, Moawad AH, Iams JD, VanDorsten P, Paul RH, Dombrowski MP, Roberts JM, McNellis D for the NICHD Maternal Fetal Medicine Units Network. ***The impact of digital cervical examination on expectantly managed preterm ruptured membranes.*** *Am J Obstet Gynecol*, 283(4):1003-1007; 2000.

Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM, Heine RP, Nugent RP, Fischer ML, Leveno KJ, Wapner R, Varner M, Trout W, Moawad A, Sibai BM, Miodovnik M, Dombrowski M, O'Sullivan MJ, VanDorsten JP, Langer O, Roberts J for the NICHD Maternal Fetal Medicine Units Network. ***Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis.*** *NEJM*, 342(8):534-540, 2000.

Mercer BM, Goldenberg, RL, Meis PJ, Moawad A, Shellhaas C, Das A, Menard K, Caritis S, Thurnau G, Dombrowski MP, Miodovnik M, Roberts JM, McNellis D for the NICHD Maternal Fetal Medicine Units Network. ***The Preterm Prediction Study: Prediction of preterm premature rupture of the membranes through clinical findings and ancillary testing.*** *Am J Obstet Gynecol*, 183(3):738-745; 2000.

Andrews WW, Goldenberg RL, Mercer BM, Moawad A, Das A, Van Dorsten P, Caritis S, Thurnau G, Miodovnik M, Roberts JM, McNellis D for the NICHD Maternal Fetal Medicine Units Network. ***The Preterm Prediction Study: Association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth.*** *Am J Obstet Gynecol*, 183(3):662-668; 2000.

**Review, cont'd**

PIs at the centers. Summary statement should arrive in about six weeks. However, the details of which centers will be included in the Network will not be known until after the National Advisory Child Health and Human Development Council meeting January 25-26. In addition to using the scientific and technical merit scores as determined by the peer reviewers, the Council will also consider program balance and the need for diversity in the study population. Availability of funds is also a factor in the final decision.

**Network Approves Two Protocols**

At their October steering committee meeting, Network PIs approved two new RCTs. The first is a trial to study whether a new FDA-approved device, which measures fetal oxygen saturation levels during labor, when used with traditional fetal heart rate monitoring, will actually lead to a reduction in overall cesarean rates. The Network trial will address several questions left unanswered by studies leading to the FDA approval. Chiefly, what was the significance of a 50% reduction in cesarean delivery for fetal distress when the rate of cesarean deliveries for dystocia doubled? In the device labeling statement, the FDA also stated an unanswered safety issue, whether withholding cesarean delivery in the face of an abnormal fetal heart rate pattern when fetal oximetry values are normal is safe or not.

The proposed 3-arm study will permit assessment of the effects of fetal oximetry on cesarean rates and infant safety in addition to maternal-fetal infections and dystocia. A sample size of 10,000 nulliparous pregnant women will be randomized over 3 years, including a preliminary 6 month training and implementation phase for research nurses. The FDA has indicated their interest and assistance in the conduct of this trial. The Data and Safety Monitoring Committee has given it a highly positive approval. Dr. Steven Bloom from UT-Southwestern Medical Center is the PI for this study.

The second trial approved by the Network involves the use of pharmacotherapies to reduce smoking and increase birth weight during pregnancy. This double-masked placebo controlled trial will enroll 1800 women at 12-20 weeks pregnant who are heavy smokers to receive either low dose nicotine replacement therapy along with smoking cessation counseling, bupropion along with smoking cessation counseling, or counseling and placebo (one-half with nicotine patch placebo and one-half with a bupropion placebo). To assess whether pharmacologic treatment of pregnant smokers is safe and effective, mothers and infants will be followed through 6 months postpartum to determine smoking status, level of depression and weight variance. Dr. Robert Goldenberg from the U. of Alabama is the PI for this study

**BEAM Trial Hits Half-Way Mark**

Eleven hundred of the twenty two hundred patients needed to meet the sample size have been recruited for the BEAM Trial. The number of infants being seen for follow-up visits is increasing and persistence in finding "lost" patients is paying off. Jane McKeever, follow-up coordinator at Tennessee, has helped Wayne State achieve a 100% follow-up rate by tracking down one of their patients who moved to Arkansas and then, using great persuasion, getting her to make the trip to Memphis for the exam. Jane also tracked down another patient by calling the patient's sister on a Sunday afternoon, and has made the suggestion that coordinators try making calls on "off hours" when people tend to be at home.

Over 800 infants now have had their cranial ultrasounds reviewed. The BCC will be contacting each center soon to request ultrasounds that were done for clinical reasons, but not sent to the BCC, be submitted. The reviewers, Drs. Bulas, Dipietro and Seibert, feel *all* ultrasounds done on infants need to be examined in order to make necessary inferences. Another review session is scheduled for February 5-6 to re-assess those infants who have these additional ultrasounds.

Two more training sessions at the Kennedy Krieger Institute are being scheduled for this winter and early spring. One will be a two-day session, attended on the first day by new follow-up examiners, including those from the 3 ancillary centers in NYC, Providence and Galveston, as well as previously certified examiners on the second day. The other session will be an annual review held for current examiners who were not able to make the first meeting.

**Factor V Leiden Study Recruitment to be Re-evaluated**

As the study is designed, no center can enroll more than 15% of the patient population (750) in order to ensure diversity. The University of Texas Southwestern Medical Center has nearly reached that limit. It is expected that the Subcommittee will undertake an evaluation of the population sample to assess whether that criteria remains necessary. About 70 carriers out of the 100 needed have already been identified, so the study is progressing very nicely.

**C-Section Study Scaled Back**

Beginning January 1, 2001, only data on delivered patients who have had prior C-Sections or VBACs will be collected. Since data will no longer be collected on patients with primary C-Sections and non-VBAC vaginal deliveries by insurance type, the Delivery Count Log is being revised and will be distributed prior to January 1. Only about half the number of patients currently being enrolled will now be eligible, radically reducing the amount of data entry required.

## Gestational Diabetes Study Update

Following a review of the protocol by the Data and Safety Monitoring Committee earlier this fall, the subcommittee for the gestational diabetes trial revised the study's primary outcome after the last Steering Committee meeting, to be a reduction in the incidence of large for gestational age. As customary, the DSMC reviewed the revision and held a conference call on November 22. They concluded that a health-based, rather than size-based, primary outcome would be preferable. Since there is little data on whether this is feasible, a pilot study was suggested. The subcommittee is taking the recommendation under consideration and will make a proposal at the next Steering Committee meeting.

## Dinner Plans Being Made

A special dinner is being planned for attendees of the next Steering Committee meeting to celebrate the accomplishments of the last five years of the NICHD MFMU Network. The event will be held January 11, the evening of the first day of the meeting. Details will be forthcoming, but in the meantime, everyone is urged to plan to attend.

## New Acting Director Named for Center for Research for Mothers and Children

Anne Willoughby, MD, MPH, has been named to replace Owen Rennert as Acting Director of the Center for Research for Mothers and Children, following Dr. Rennert's appointment as Director of the Division of Intramural Research and Scientific Director for NICHD. Dr. Willoughby is also the Chief of the Pediatric, Adolescent and Maternal AIDS Branch of the Center for Research for Mothers and Children of NICHD. As such, she supervises the conduct and support of research on the epidemiology, natural history, pathogenesis, clinical manifestations, treatment and prevention of HIV infection and disease in pregnant women, mothers, women of reproductive age, infants, children, adolescents and families.

Dr. Willoughby completed her college education at Bryn Mawr College and then received the MD degree from Cornell University Medical College. She served as a Robert Wood Johnson General Pediatric Academic Fellow at Stanford University and then received a MPH in epidemiology from the University of California at Berkeley. She has been at the NIH for sixteen years, serving as an Epidemiology Fellow and then as Special Assistant for Pediatrics in the Pregnancy and Perinatology Branch.

## People in the News

- \* Congratulations to **Kevin Pinder**, BCC secretary, who was married November 25. After spending a wonderful honeymoon in Jamaica, his feet are back on the ground and he is hard at work in the office.
- \* Best wishes to **Wendy Knox**, nee **Girdler**, research nurse at the U. of Cincinnati, who was married September 24. Despite having a rainy day for her outdoor wedding and reception, Wendy reports the event was marvelous and her honeymoon to Hawaii was blissful.
- \* Congratulations to C-Section nurse at Wake Forest, **Christie Lanier**, who gave birth to a 7 lb 13 oz daughter on October 4. As a repeat c-section herself, Christie was enrolled in the C-Section study, though Missy Swain wouldn't give her a break and made her complete all her own data forms!

## Calendar of Events



### Steering Committee Meetings

January 11-12, 2001

April 5-6, 2001

July 16-17, 2001

October 18-19, 2001

THE WIZARD OF ID Parker & Hart

Best Wishes for Merry  
Holidays  
and  
A Happy, Healthy New Year!

On the  
Light  
Side

