



# The MFMU Networker

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## NIH Consensus Conference Concludes More Research Needed on Antenatal Steroids

For the first time ever, a NIH Consensus Panel was asked to reconvene for a follow-up conference to consider whether questions and issues raised during the original conference had since been resolved. In 1994, the NIH sponsored a Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes to assess the effectiveness of antenatal glucocorticoid therapy. The consensus panel concluded that giving a single dose of corticosteroids to women at risk for preterm delivery reduces the risk of death, respiratory distress syndrome and intraventricular hemorrhage in their preterm infants. While making this recommendation however, the Panel also noted that the potential benefits and risks of repeated administration of corticosteroids were unknown and identified areas of future research.

During recent years, the use of repeat courses of antenatal corticosteroids has become widespread in clinical practice. Published data from some studies report, both, no benefit and potential harm from additional doses of steroids. While there are no published trials, there are several randomized clinical trials underway, including the one being conducted by the NICHD MFMU Network. Because of the conflicting data, the NIH reconvened the original Consensus Panel, consisting of fifteen independent, non-Federal professionals in specialized fields such as, OBGYN, MFM, Reproductive Sciences, Neonatology, Pediatrics, Behavioral Health, Pharmacology, and Biostatistics.

Following one and a half days of presentations by experts in related fields, as well as receiving questions and comments from the public, the Consensus Panel determined that "data from currently available studies assessing benefits and risks are inadequate to argue for or against the use of repeat or rescue courses of antenatal corticosteroids in clinical practice".

The panel also drew three conclusions from the conference:

1. The collective international data continue to strongly support the use and efficacy of a single course of antenatal corticosteroids, using the dosage and interval of administration specified in the 1994 Consensus Development Conference report;
2. The current benefit and risk data are insufficient to support the routine use of repeat or rescue courses of corticosteroids in clinical practice; and
3. Clinical trials are in progress to assess potential benefits and risks of various regimens of repeat corticosteroids. Until data establish a favorable benefit-to-risk ratio, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials.

The conference has cleared the way for the MFMU Network's trial of Antenatal Corticosteroids Regimens to proceed. It is anticipated that, since the panel recommended restricting corticosteroid administration to a single course, doctors, especially those who practice rescue or multiple dosing, will be more interested in promoting recruitment to the trial.

## Primary Outcome Revised for Gestational Diabetes Trial

The subcommittee has approved a revision of the primary research outcome for the next Network trial, scheduled to begin this fall. Rather than addressing whether "diet treatment compared with standard OB care for low risk pregnancies reduces the risk for large for age gestational infants", the question now asks whether "diet treatment and monitoring applied to women with a singleton pregnancy, diagnosed with mild gestational diabetes between 24 and 29 weeks GA, reduce the incidence of *macrosomia* (birth weight greater than 4000 grams) as compared to standard obstetrical care".

The study is a combination of a randomized multi-center clinical trial and an observational cohort, involving 2000 pregnant women. A total of four groups will be enrolled. Eight hundred women with mild GDM, defined as a positive GLT with a subsequent abnormal OGTT, will be randomized to one of two treatment/non-treatment groups. Another 800 women with a positive GLT but subsequent normal OGTT will be enrolled in an observational cohort, matched by race and body mass index to the patients in the randomized trial. The final group consists of 400 non-diabetic controls enrolled in race/body mass index categories determined by racial distribution among gestational diabetics at each center.

Certification training for Coordinators will take place on October 18, following the 2-day Steering Committee meeting. A representative from Quest Diagnostics (formerly Smith Kline Beecham) will be present to cover the logistics of the central OGTT analyses.

## Bears Visit 12<sup>th</sup> Annual NICHD Aspen Conference

Participants in the annual Conference on Maternal-Fetal/Neonatal/Reproductive Medicine, held August 23-26, had to beware of the bears as they attended the lectures and workshops geared to promoting investigative careers in OB/GYN. To the delight of her daughter, Dr. Cathy Spong was one of the attendees who sighted a mother and cub on the grounds of the Given Institute in Aspen.

The goal of the Institute each year is to promote investigative careers in OB/GYN to about 65 clinical fellows in maternal fetal medicine, neonatology, and reproductive endocrinology. Familiar faces from the NICHD and the Network, who were presenters or led sessions, included Robert Goldenberg, Steven Gabbe, Elizabeth Thom, Cathy

Spong, Susie Meikle, Charlotte Catz, Linda Wright, Sumner Yaffe, and Duane Alexander. Among the highlights, Cathy Spong presented the results of her study of Prevention of Fetal Alcohol Syndrome in an Animal Model during a session on reproductive biology and endocrinology. Steve Gabbe presented an overview of the problems in defining gestational diabetes and the implications of the disease in preparation for a clinical trials workshop which focused on the design of a treatment trial of mild gestational diabetes. As a result of the workshop, Cathy Spong, Steve Gabbe, and Liz Thom proposed the change to the primary outcome of the Network's gestational diabetes trial.

### 16 Abstracts Submitted to SMFM

This fall was busy for MFMU Network investigators and BCC statisticians as they worked on the largest number of abstract analyses submitted since 1997 for the Society of Maternal Fetal Medicine's 2001 meeting. While the new computerized system, implemented by SMFM for submitting abstracts, created some challenges, the following 16 presentations and posters were submitted by the August 11 deadline:

#### From the Preterm Prediction Singleton Study

Ramsey PS. *The Preterm Prediction Study: Cervical human chorionic gonadotropin levels and spontaneous preterm birth in asymptomatic women.*

Ramsey PS. *The Preterm Prediction Study: Cervical alpha-fetoprotein levels and spontaneous preterm birth in asymptomatic women.*

Ramsey PS. *Serologic markers at 22-24 weeks' gestation improve the prediction of subsequent spontaneous preterm birth.*

#### From the High Risk Aspirin trial

Sibai B, Romero R. *Plasma concentrations of the soluble tumor necrosis factor receptor 2 are increased prior to the development of preeclampsia.*

Romero R, Sibai B. *Changes in the maternal plasma concentration of two angiogenic factors - placental growth factor and angiogenin - preceded the development of preeclampsia.*

Lain K, Caritis S. *Elevated cellular adhesion molecule concentrations in mid-pregnancy may predict recurrent preeclampsia.*

Branch W. *Antiphospholipid antibodies in women at risk for preeclampsia.*

Hnat M. *Perinatal outcome in women with recurrent preeclampsia compared to those who develop preeclampsia as nullipara.*

Myatt L. *Do women at high risk develop preeclampsia earlier in gestation than those at low risk?*

Hogg B. *The influence of gestational age on the effectiveness of low-dose aspirin for the prevention of hypertensive disease and growth restriction in pregnancy.*

#### From the HUAM study

Newman R. *Uterine activity during pregnancy: singleton vs twin gestations.*

Newman R. *Uterine contraction frequency does not predict preterm birth in twins.*

#### From the BV trial

Berghella V. *Sexual behavior, BV and PTD.*

Sheffield JS. *The effect of bacterial vaginosis treatment on the acquisition of other symptomatic sexually transmitted diseases during pregnancy.*

#### From the Asthma Observational study

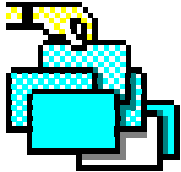
Landon MB. *Treatment regimen is more predictive of asthma severity during pregnancy than current NAEP.*

#### From the Asthma RCT

Dombrowski M. *Randomized trial of inhaled beclomethasone vs theophylline for asthma during pregnancy.*

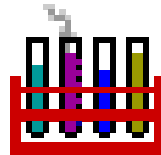
## RFA Update

Numerous applications were received by the July 11, 2000 deadline for the Cooperative Multicenter MFMU Network RFA. Established in 1986, this Cooperative Agreement (U10) is intended to be an assistance mechanism to support the recipient's involvement in the ongoing multicenter clinical program. It is expected that 13 centers will be selected to participate in the Network's 3<sup>rd</sup> competitive cycle for the next 5-year project period beginning April 1, 2001. To date, the applications are being processed by the Center for Scientific Review. The official review is planned for late October, after which a presentation will be made to the January 2001 NICHD Council naming the selected applicants. We look forward to notifying the Steering Committee and any new applicants as soon as the "new" Network is selected.



## Factor V Study Exceeding Enrollment Expectations

The prevalence of the factor V Leiden mutation in pregnant women being screened for this study is 26% higher than predicted. The first deliveries will be in mid-October and nurses should be making preparations for ensuring cord blood and placentas are collected. Cord blood needs to be obtained from all infants. A new software report will be available for identifying, within specific time periods, those 300 patients in the carrier/control groups from whom placentas need to be collected. The study investigators stress that it is very important to obtain complete information on patients.



## Advisory Board Approves New Mini-Protocols

The Advisory Board held a conference call in September to review two approved Network mini protocols, Fetal Pulse Oximeter and Smoking Cessation. The Board provided a very constructive review of the protocols presenting critical points of view for consideration. The advice of the Advisory Board will be taken into consideration and aid in continued protocol development. Revised mini protocols will be presented at the next Steering Committee meeting pending approval and possible advancement to the protocol stage. While the Network has several new concepts in the works, there are currently no new mini protocols on the horizon, so the Advisory Board will be in recess until after the January Steering Committee meeting. It is anticipated that the membership composition of the Advisory Board will be revisited once the new Network is established and likely that a new Chairperson will be appointed at that time.

## DHHS Announces Initiatives to Protect Research Subjects

In the September 14 issue of the *NEJM*, Donna Shalala, secretary of health and human services, outlined steps being taken by her agency to strengthen protections for human subjects as a result of recent trends in clinical research. Investigations undertaken by the NIH and the FDA since the death of a patient in a gene transfer trial have uncovered numerous breaches in the current system of protections. These discoveries involve incidences of disturbing recruitment practices and non-adherence to standards of good clinical practice such as failure to disqualify ineligible subjects, failure to report adverse events, failure to ensure protocols are followed, and failure to ensure study staff has adequate training. The other areas of concern include the increasing pressures on IRBs and the rising number of conflicts of interest and ethical dilemmas facing academic researchers as the boundaries between industry and academic medicine blur.

On May 23, the DHHS announced a number of steps to strengthen and improve the current system of protections to ensure the safety of subjects in clinical trials. First, the NIH and the FDA will require all clinical investigators to receive training in bioethics and other issues related to human research. Second, the NIH and the FDA will issue specific guidelines on informed consent procedures. Third, in addition to requiring investigators who conduct small-scale early clinical trials to submit monitoring plans at the time they

submit their grant applications, the FDA will issue new guidelines for data and safety monitoring boards (DSMBs). These guidelines will specify the relationship between DSMBs and IRBs, cover membership of the DSMBs as well as how they operate, their responsibilities and their obligations to maintain patients' confidentiality. Fourth, regulations relating to conflicts of interest will be clarified. And, fifth, legislation will be introduced to enable the FDA to levy civil monetary penalties for violations of informed consent and other research practices.

To oversee these reforms, the role of the Office for Protection from Research Risks (OPRR) of the NIH has been expanded and its responsibilities transferred to the Office of the Secretary where it has been renamed the Office for Human Research Protections. Dr. Shalala states that the government alone cannot adequately protect human research subjects. She challenges everyone involved in the oversight of clinical research to take the responsibility and necessary actions to strengthen the conduct of research at their institutions. The implications of all this on the NICHD MFMU Network has yet to be determined. However, a few of participating MFMU centers have had to suspend research recently while their university IRBs and research practices were subjected to federal scrutiny.

## People in the News

◆ We will miss working with **Susan Barker**, coordinator from San Antonio, who has left her position to take up a life long dream of studying graphic arts. We welcome **Mary Sueltenfuss**, the new coordinator, and look forward to meeting her at the next Steering Committee meeting. Mary will also be visiting the BCC for a 2-1/2 day training session at the end of September.

◆ **Michele Thierren** left the BCC at the end of August to take a position as research project coordinator at another health research firm. She recently received her masters in Epidemiology from GWU. Kevin Kiger has assumed responsibility as the RA for the Factor V Leiden study.

◆ Congratulations to **Michelle DiVito**, coordinator at Thomas Jefferson, on the birth of her twins, Alana and Andrew, born July 20. They weighed 5,1 and 5,0 respectively - a lot of baby for our petite Michelle! According to Dr. Wapner, it's been difficult to keep her away from work, but **Mary Talucci** has done a great job filling in while she's on maternity leave until October.

◆ The BCC welcomes **Ralph Kolva** as the newest member of the Network's Software team. A person of many interests and talents, this is Ralph's third career move, following small business management and residential appraising. He has always had his hand in the computer field and decided to make it an official career as he finishes his computer science degree from U. Maryland. He likes woodworking (like Brendan!) and has even crafted canoes. He also enjoys hiking, climbing, biking, travel and calls himself an architectural history buff.

◆ **Christopher Myers** is the new NICHD grants management specialist for the Network, replacing Carolyn Kofa. He comes to the position with lots of experience at NIH in grants and contracts and we know Kimberly Howell especially was pleased with his assistance in getting the Network's 2000-2001 budget established. Kudos to **Kim Howell** for her incredibly hard work and attention to detail in preparing and getting out the MFMU awards this year. Without her dedication and quick study of grants management, the job could have still been incomplete!

**WANTED by the BCC**...used medical books, including texts, references, dictionaries, etc. While a little knowledge may be considered dangerous, not being able to easily research maternal and fetal medical subjects is considerably frustrating for the staff at the BCC as they work on protocol and manual development and edit data. Any relevant books that you could contribute for their reference would be greatly appreciated!

## Calendar of Events



### *Steering Committee Meetings*

October 16-17, 2000

January 11-12, 2001

April 5-6, 2001

July 16-17, 2001

October 18-19, 2001

### *Gestational Diabetes Certification Training*

October 18, 2000

### *BEAM Ultrasound Reviews*

October 5-6, 2000

November 16-17, 2000

### *SGI Abstract Schedule*

October 19 - Abstracts submitted to Dr. Paul Meis

October ? - Conference call to be scheduled

October 26 - Abstracts due at SGI

### *Data and Safety Monitoring Committee Meeting*

October 3, 2000