Pregnancy and Perinatology Branch (PPB) NICHD

Report to the NACHHD Council September 2008

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Eunice Kennedy Shriver National Institute of Child Health and Human Development

TABLE OF CONTENTS

PPB MAJOR MILESTONES AND ADVANCES: 2004-2007

2004

- January—NICHD-AAP Research & Training in Neonatology Workshop: Ariagno et al. (2005). *Pediatrics, Feb;115*(2), 475-479; Raju et al. (2005). *Pediatrics Feb;115*(2), 468-474.
- January—NICHD-USAID Periconceptional Nutrition and Pregnancy Outcome Workshop
- January—PPB Strategic Plan distributed to the NACHHD Council
- January—Fetal growth restriction RFA presented to NACHHD Council
- March—Border of Viability Workshop: Higgins et al. (2005). *Pediatrics, 115*, 1392-1396.
- March—Long-term Followup of Prenatal Drug Exposure: Challenges and Opportunities Workshop
- April—Condon et al. (2004). Surfactant protein secreted by the maturing mouse fetal lung acts as a hormone that signals the initiation of parturition. *PNAS, 101*, 4978-4983.
- May—Anand et al. (2004). Effects of preemptive morphine analgesia (NEOPAIN trial). *Lancet, 363*, 1673-1682.
- May—Poindexter et al. (2004). Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants. *Pediatrics, 113*, 1209-1215.
- August—Fetal Treatment: Needs Assessment and Future Directions Workshop
- November—Improving Maternal & Infant Nutrition: Development of a Research Plan
- December—Prenatal Screening: Incorporating the First Trimester Studies Conference: Reddy et al. (2006). *Obstet Gynecol*, 107, 167-173.
- December—Landon et al. (2004). Maternal and perinatal outcome in women undergoing trial of labor after cesarean delivery. *NEJM, 351*, 2581-2589.

2005

- January—State-of-the-Science Conference: Maternal Request Cesarean Delivery (planning meeting)
- May—Hypothermia for Perinatal Asphyxia Workshop; Higgins et al. (2006). *J Pediatr, Feb;148*(2), 170-175.
- July—Near-term pregnancy and near-term newborn infant: Optimizing care and long-term outcomes: Raju et al. (2006). *Pediatrics, Sep;118*(3), 1207-1214; 17 papers in two issues of *Seminars in Perinatology*, February and March, 2006.
- July—Van Meurs et al. (2005). Inhaled nitric oxide for premature infants with severe respiratory failure. *NEJM 7;*353(1), 13-22.
- August—Oxygen in Babies Conference: Higgins et al. (2007). *Pediatrics, Apr;119*(4), 790-796.
- September—Infertility Treatment and Adverse Pregnancy Outcome Workshop: Reddy et al. (2007). *Obstet Gynecol*, 109, 967-977.
- October—Shankaran et al. (2005). Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *NEJM, 13;*353(15), 1574-1584.

2006

- February—Higgins et al. (2006). Hypothermia and perinatal outcome. *Pediatr,* 148(2), 170-175.
- March—State-of-the-Science Conference: Cesarean Delivery on Maternal Request
- March—Mullany et al. (2006). Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: A community-based, cluster-randomised trial. *Lancet, 18;367*(9514), 910-988.
- June—Silver et al. (2006). Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol,* 107(6), 1226-1232.
- June—Consensus Statement Maternal Request Cesarean Delivery. *Obstet Gynecol, 107*(6), 1386-1397.
- July—Landon et al. (2006). Risk of uterine rupture with a trial of labor in women with multiple and single prior cesarean delivery. *Obstet Gynecol*, 108(1), 12-20.

- July—Bloom et al. (2006). Decision-to-incision times and maternal and infant outcomes. *Obstet Gynecol, 108*, 6-11.
- August—Perinatal Stroke Workshop: Raju et al. (2007). *Pediatrics, Sep;120*(3), 609-616.
- September—Prenatal Imaging: Ultrasound and MRI Workshop: Reddy et al. (2008).*Obstet Gynecol*, *112*, 145-157.
- October—Bloom et al. (2006). Fetal pulse oximetry and cesarean delivery. *NEJM 23;355*(21), 2195-2202.

2007

- March—Egyptian Bilirubin Meeting: White paper submitted to the NACHHD Council (June)
- August—Antepartum Fetal Monitoring Workshop
- August—PASS Network Phase II Patient Recruitment Begins
- August—Rouse et al. (2007). A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *NEJM, 2;*357(5), 454-461.
- September—International Stillbirth Workshop: Research Definitions
- September—Wapner et al. (2007). Long-term outcomes after repeat doses of antenatal corticosteroids. *NEJM, 20;357*(12), 1190-1198.
- October—Northen et al. (2007). Followup of children exposed *in utero* to 17 alpha-hydroxyprogesterone caproate compared with placebo. *Obstet Gynecol, Oct;110*(4), 865-872.
- October—Vaginal Birth After Cesarean Consensus Development Conference (organizational meeting)

2008

- January—Initiation of Institute of Medicine Panel: Reevaluation of Pregnancy Weight Gain Guidelines
- March—Breastfeeding patterns, time to initiation, mortality risk among newborns in Southern Nepal. *J Nutr, 138*, 599-603.
- April—Preconception Care Workshop
- April—Tyson et al. Intensive care for extreme prematurity: Moving beyond gestational age. *NEJM, 358*(16), 1672-1681.
- April—PPB Expert Panel Review
- April—Electronic Fetal Heart Rate Monitoring Workshop: A Reevaluation
- June: Surgeon General's Conference on the Prevention of Preterm Birth
- August—Neonatal Infection Workshop
- August—Vaginal Birth After Cesarean Consensus Development Conference (planning meeting)
- August—Antenatal Testing: A Reevaluation, Special Issue of *Seminars in Perinatology*
- September—Neonatal Hypoglycemia Workshop

EXECUTIVE SUMMARY

The mission of the Pregnancy and Perinatology Branch (PPB), within the Center for Developmental Biology and Perinatal Medicine (CDBPM), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), is to improve the health of mothers and children with a focus on maternal health, pregnancy, fetal well-being, labor and delivery, and the developing child. The Branch seeks to acquire scientific information that supports its mission through basic and clinical research, including: determining basic mechanisms that underlie normal and disease processes; identifying new treatments, methodologies, and preventive strategies that arise from translational and evidence-based research; assessing the dissemination and impact of therapeutic and preventive interventions; and increasing scientific resources through recruitment and training of investigators.

Since its last report to the National Advisory Child Health and Human Development (NACHHD) Council, Branch funding has remained relatively stable. The PPB utilizes many existing National Institutes of Health (NIH) funding mechanisms to support its activities, which extend from basic research to clinical trials (see Figure 1).

During the past four years, the Branch has expanded significantly, making considerable strides in incorporating the obstetric, neonatal, and basic science fields. The Branch's long-term efforts, the Neonatal Research Network (NRN) and Maternal-Fetal Medicine Units (MFMU) Network, continue to be very successful. Each year, Network researchers have each given more than 20 national presentations, have had publications in top-tier journals, and have provided data used by professional organizations to guide clinical practice. In addition, through the success of a number of initiatives, the Branch has expanded its portfolio to extend and enhance research in fetal surgery, stillbirth, periconceptional alcohol exposure, sudden infant death syndrome (SIDS), health disparities and preterm birth, and perinatal genetics. (See Appendix B for a listing of PPB-supported studies and trials that have impacted clinical practice.)

Branch activities are organized around five maternal-fetal emphasis areas, which complement each other and build a comprehensive approach to research during the pre-, peri-, and postnatal periods: High-risk pregnancy, fetal pathophysiology, preterm labor and birth, disorders of the newborn, and SIDS.

The Branch has successfully launched and maintained several time-limited networks, including the Management of Myelomeningocele Study (MOMS) Network, the Community Child Health Network (CCHN), the Stillbirth Collaborative Research Network (SCRN), the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network, and the Genomics and Proteomics Network for Preterm Birth Research (GPN/PBR). Several of these networks are the result of collaborations, including a few with other NICHD Centers (e.g., CCHN is done in conjunction with the Center for Population Research) and with other Institutes (e.g., PASS is maintained in conjunction with the National Institute on Alcohol Abuse and Alcoholism; CCHN in conjunction with the National Institute of Nursing Research). The Branch also has significant interactions and partnerships with many other agencies and NIH Institutes.

The Branch members also serve as members of committees for other NIH Institutes, such as the Trans-NIH Liver Diseases Subcommittee for the National Institute of Diabetes and Digestive and Kidney Diseases, and the Pre and Probiotic Working Group for the National Institute of Allergy and Infectious Diseases. In 2006, one Branch member completed a detail at the NIH Office of Extramural Research. Branch members also serve as liaisons to major societies in their respective fields.

In December 2002, the Branch held a two-day workshop to develop a strategic research plan for 2005 to 2010. The results from this workshop were published as the *Pregnancy and Perinatology Branch, NICHD, A Strategic Plan, 2005-2010*. In 2008, as part of the Institute's continued efforts to improve strategic planning for its components, the PPB sought advice and feedback from a panel of experts about its possible future research directions for 2009 through 2013. The panel included experts in the fields of neonatology, pediatrics, maternal-fetal medicine, obstetrics, and epidemiology and included members of the NACHHD Council (see Appendix G for a list of members). The panel continued the review and analysis of the Branch portfolio that was initiated in 2002. The results of the panel's analysis are included in the *Future Directions for the PPB* section of this report.

The PPB is convinced that investing efforts and funds in basic and clinical research for mothers' and infants' health problems will result in significant savings of later expenses for the care of patients who develop preventable disabilities and/or diseases. Most importantly, these investments will help promote the birth of healthy infants, who are able to achieve their full potential for healthy and productive lives.

INTRODUCTION TO THE BRANCH

The Pregnancy and Perinatology Branch (PPB), within the Center for Developmental Biology and Perinatal Medicine (CDBPM), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), seeks to improve the health of mothers and children by focusing on maternal health, pregnancy, fetal well-being, labor and delivery, and the developing child. The Branch seeks to acquire scientific information supporting its mission through basic and clinical research, including: determining basic mechanisms that underlie normal and disease processes; identifying new treatments, methodologies, and preventive strategies that arise from translational and evidence-based research; assessing the dissemination and impact of therapeutic and preventive interventions; and increasing scientific resources through recruitment and training of investigators.

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continue to be very successful. Each year, Network researchers have each given more than 20 national presentations, have had publications in top-tier journals, and have provided data used by professional organizations to guide clinical practice. In addition, through the success of a number of initiatives, the Branch has expanded its portfolio to extend and enhance research in fetal surgery, stillbirth, periconceptional alcohol exposure, sudden infant death syndrome (SIDS), health disparities and preterm birth, and perinatal genetics. (See Appendix B for a listing of PPB-supported studies and trials that have impacted clinical practice.)

Branch activities are organized around the following five maternal-fetal emphasis areas, which complement each other and build a comprehensive approach to research during the pre-, peri-, and postnatal periods:

- **High-risk pregnancy** is concerned with those factors, both normal and abnormal, influencing the course and outcome of pregnancy; factors include maternal physiology, environmental variables, conditions, and treatments that occur during pregnancy, all of which contribute to adverse outcomes (e.g., low birth weight). Studies in this area include (but are not limited to) elucidating: mechanisms involved in the pathophysiological states of pregnancy; health impact of pregnancy-related disorders on mother and infant; pathogenesis of symptomatic and asymptomatic maternal infections and their effects on fetal development, with the aim of improving treatment and prevention; effects of maternal medications and mother's use and abuse of drugs on fetal development; and adolescent pregnancy.
- **Fetal pathophysiology** includes studies of the physiologic, metabolic, endocrine, and pharmacologic events related to abnormal development of the fetus; such events include morphology, function, and metabolism of the placenta and uterine blood flow. The Branch encourages studies in this area to improve existing methodologies for antenatal diagnosis regarding fetal status, growth, position, maturity, and well-being.
- **Preterm labor and birth** promotes studies of the factors affecting the initiation and completion of labor, as well as the physiology, endocrinology, and pharmacology of parturition. Of special concern are causes and prevention of preterm labor, threatened and habitual pregnancy loss (miscarriage), prolonged and dysfunctional labor, and dystocia.
- **Disorders of the newborn** includes basic and clinical studies concerned with the etiology, pathophysiology, therapy, and followup of conditions, such as adaptation to extrauterine life, hyperbilirubinemia, and sequelae of prematurity (i.e., asphyxia, respiratory distress, bronchopulmonary dysplasia, hypoglycemia, anemia, and infection), that are associated with the perinatal and neonatal period.
- **SIDS** encompasses studies to elucidate underlying mechanisms of SIDS and its probable cause(s). Additional research strives to identify infants at risk for SIDS and to develop preventive approaches.

Since its last report to the National Advisory Child Health and Human Development (NACHHD) Council, the Branch has successfully launched and maintained several time-limited networks, including the Management of Myelomeningocele Surgery (MOMS) Network, the Community Child Health Network (CCHN), the Stillbirth Collaborative Research Network (SCRN), the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network, and the Genomics and Proteomics Network for Preterm Birth Research (GPN/PBR). Several of these networks are the result of

collaborations with other NICHD Centers (e.g., CCHN efforts is in conjunction with the Center for Population Research) and with other Institutes and agencies (see below).

The Branch members also serve as liaisons to major societies in their respective fields, including: Section on Perinatal Pediatrics of the American Academy of Pediatrics (AAP); the AAP Committee on the Fetus and Newborn; the Society for Maternal-Fetal Medicine (SMFM); the American College of Obstetricians and Gynecologists (ACOG); the Liaison Committee for Obstetricians and Gynecologists. Branch members have also served in advisory capacities for professional groups, such as the Cochrane Collaboration Child Health Advisory Board and the Vermont Oxford Network.

The Branch has had significant interactions and partnerships with other Institutes and agencies, including (but not limited to):

- U.S. Department of Health and Human Services (DHHS) Interagency Coordinating Council on Low Birth Weight and Preterm Birth
- Centers for Disease Control and Prevention (CDC)—NRN Cytokine Analysis and Early Onset Sepsis Surveillance Study, Stillbirth Research, and Preconception Care
- U.S. Food and Drug Administration (FDA)
  - With the NIH Office of Research on Women's Health (ORWH)—Best Pharmaceuticals for Children Act (BPCA) Activities, the Breastfeeding Survey, Pregnancy Food Pyramid (part of http://MyPyramid.gov)
  - With the MFMU Network and the NRN—Development and Testing of Equipment and Investigational Drugs
  - Infant Feeding Practices Study II: NICHD co-funded this study, which was led by the FDA; the study was completed in 2007, and the first set of 13 papers will be published in a supplement to *Pediatrics* in October 2008.
- National Institute of Mental Health (NIMH)—co-sponsor of the program announcement (PA) Women's Mental Health in Pregnancy and the Postpartum Period
- National Institute of Neurological Disorders and Stroke (NINDS)—co-sponsor of MFMU Network studies
- National Heart, Lung, and Blood Institute (NHLBI)—co-sponsor NRN and MFMU Network studies
- National Eye Institute (NEI)—co-sponsor of NRN studies
- NIH ORWH—co-sponsor of MFMU Network studies
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)—co-funder of the PASS Network
- National Institute of Nursing Research (NINR)—co-funder of the CCHN
- National Institute on Drug Abuse (NIDA)—co-funder of the Maternal Lifestyles Study

The Branch is among the largest sources of support for research on pregnancy and perinatology. Using a combination of funding and training mechanisms, the PPB supported 302 projects for a total of more than $94 million (see Table 1, Figure 1, Figure 2, and Figure 3) in fiscal year 2007.

In addition to the extensive strategic planning process the Branch went through in 2002, in 2008, the PPB also relied on an expert panel to review its portfolio, analyze its activities, and recommend future research directions for the Branch. The panel included experts in fields relevant to Branch-supported research, public and patient advocates, and members of the NACHHD Council (see Appendix G for a list of panel members). The results of the panel's analysis are included in the *Future Directions for the PPB* section of this report.

The remainder of this report describes the Branch's activities, including Branch-supported grants and contracts in the five research areas explained above, cooperative agreements, research networks, and other activities since the Branch's last report to the NACHHD Council.

BRANCH ACTIVITIES: RESEARCH PROJECT GRANTS AND CONTRACTS

The following section highlights a few of the advances in each Branch research category; due to space limitations, all the advances could not be included in this report. Highlights from Branch-supported research networks are summarized separately.

MATERNAL RESEARCH

This portfolio includes basic, translational, and clinical research studies, which address a myriad of issues in pregnancy to understand normal and abnormal physiological events and the effects of maternal, acute, or chronic diseases on pregnancy and fetal development.

Preeclampsia

Preeclampsia is a major and potentially serious disorder of pregnancy. This hypertensive disease affects approximately 7 percent of first pregnancies and 3 percent of all pregnancies. Preeclampsia contributes significantly to preterm deliveries in the United States, and, its severest form, eclampsia, is a leading cause of maternal morbidity and mortality. Although its exact mechanism(s) is unknown, preeclampsia is widely believed to result from poor vascular development between the placenta and the uterus. In a normal pregnancy, trophoblastic cells, the main type of cell in the placenta, invade deep within the uterus and remodel small uterine arteries into large-diameter vessels. In preeclampsia, the trophoblastic cells fail to invade the uterus adequately, preventing the normal remodeling process of the uterine vessels. In turn, the poorly perfused placenta releases factors into the maternal circulation that result in the systemic symptoms of the disease.

SOLUBLE FMS-LIKE TYROSINE KINASE-1(SFLT-1)

sFlt-1 is thought to play a major role in the pathophysiology of preeclampsia, a disease characterized by severe endothelial dysfunction. Levels of sFlt-1 are dramatically increased in preeclampsia, and the increase precedes disease manifestation. Furthermore, exogenous expression of sFlt-1 in a rodent model leads to a preeclampsia-like syndrome. sFlt-1 is a soluble

form of the receptor that binds vascular endothelial growth factor (VEGF), an essential growth factor necessary for the normal functioning of endothelial cells. An abnormally high circulating level of sFlt-1 disrupts VEGF by binding to the membrane-bound form of Flt-1 on endothelial cells, leading to endothelial dysfunction. It has long been assumed that the major source of sFlt-1 production was the trophoblast cells of the placenta.

Based on the observation that rinsing placental biopsies in saline to remove excess blood resulted in an eight-fold decrease in the level of sFlt-1 mRNA, a researcher (supported through another PPB-supported investigator's grant) pursued the reason behind this serendipitous finding. He hypothesized that peripheral blood mononuclear cells (PBMCs) could be a significant source of extra-placental sFlt-1. He demonstrated that the PBMCs of normal pregnant women could produce sFlt-1, and that its production could be further stimulated under hypoxic conditions—a known inducer of sFlt-1 via the hypoxia-inducible factor-1 alpha pathway. The researcher further demonstrated that PBMCs obtained from women with preeclampsia, under normoxic conditions, produced twice the sFlt-1 of those from normal women; under hypoxic conditions, the production could be further stimulated an additional two-fold in PBMCs obtained from both normal women and women with preeclampsia. Furthermore, analysis of PBMCs obtained from women with a history of preeclampsia showed elevated production of sFlt-1 even after one year postpartum. Thus, this researcher provided the field with important information on an extra-placental source of sFlt-1.

However, many important unresolved questions about preeclampsia remain. What is the contribution of PBMCs derived sFlt-1 to the total circulating sFlt-1? Are PBMCs activated to produce abnormally high levels of sFlt-1 because of their exposure to a hypoxic placental environment, or are PBMCs of women predisposed to preeclampsia already sensitized to over react to a hypoxic placental environment? How important are activated PBMCs in driving the systemic maternal syndrome? Based on the work described above, the talented researcher is now a PPB-supported investigator who received his first NIH grant in fiscal year 2007 to answer these important questions.

THE RENIN/ANGIOTENSIN SYSTEM

This system is an important regulator of systemic blood pressure that is mediated through the production of angiotensin II (Ang II), a potent vasoconstrictor, through the action of kidney-derived renin. However, a local renin/angiotensin system is also present in many other tissues, including the placenta. Because the level of Ang II increases concomitant with sFlt-1 during pregnancy, an investigative team hypothesized that Ang II may promote the expression of sFlt-1. They demonstrated that infusing pregnant mice with Ang II resulted in an increased level of circulating sFlt-1. Furthermore, Ang II stimulated sFlt-1 production in human villous explants, as well as in purified human trophoblast cells in culture. The team also demonstrated that Ang II-mediated sFlt-1 production was mediated through the Ang II type 1 receptor. Thus, this team discovered a previously unrecognized signaling pathway involved in sFlt-1 production. The team speculates that this pathway may be important in the pathophysiology of preeclampsia. Although it is known that the levels of sFlt-1 are elevated in women with preeclampsia, while the level of Ang II is not, women with preeclampsia often show activation of autoantibodies to the Ang II type-1 receptor, which mimics the action of Ang II.

DISCOVERY OF BIOLOGICAL MARKERS

Biological markers that signal impending disease and its severity are critically important for the effective clinical management of the patient, as well as for providing a research tool that can increase the specificity of studies. One investigative team has been particularly active in studying the biological markers of preeclampsia. Hyperuricemia is common in preeclampsia and is manifested early in pregnancy. In addition, uric acid is known to promote inflammation, oxidative stress, and endothelial dysfunction, all of which are associated with preeclampsia. The investigative team hypothesized that the measurement of uric acid might be an additional marker of adverse pregnancy outcome in gestational hypertension.

They examined fetal outcome data from 972 pregnancies. Subjects were nulliparous with no known medical complications prior to pregnancy. Analytes were measured from specimens taken at admission for delivery. The frequency of preterm birth, the duration of pregnancy, frequency of small-for-gestational-age (SGA) infants, and birth weight centile were examined in the presence or absence of combinations of hypertension (H), hyperuricemia (U), and proteinuria (P). The relative risk (RR) for a preterm birth was significantly increased in the groups of women with HU (RR = 3.3) and HPU (RR = 9.7), but no significant difference was found in the other groups (H, P, U, HP, PU) compared to controls. The relative risk for an SGA infant, at less than the 5th percentile, was significantly increased in the groups of women with HU (RR = 4.6), PU (RR = 7.4), and HPU (RR = 2.2); however, researchers found no significant difference in the other groups (H, P, U, HP) compared to controls. In addition, the mean gestational age (GA) in weeks at delivery was also significantly reduced in women with HU (GA = 38.7), PU (GA = 38.0), and HPU (GA = 35.4) compared to all the other groups. Hence, the risk of these adverse outcomes increased with the incidence of hyperuricemia. The utility of the measurement of uric acid for the prediction of adverse pregnancy outcomes warrants further examination, especially for measurements taken early in pregnancy.

Exercise and Pregnancy

Regular physical activity during pregnancy and its potential to redistribute blood flow away from the uterus and viscera and to affect placental morphology and function are other areas of study for PPB-funded investigators. Pregnant women are often advised not to engage in supine exercise out of concern that direct pressure of the gravid uterus on the inferior vena cava will decrease venous return, cardiac output, and uterine blood flow. With the use of Doppler ultrasound, a PPB-supported team measured uterine artery diameter and flow rates for pregnant women (at 28 weeks to 38 weeks of gestation) at rest on their left sides and in the supine position. In addition to documenting a decrease in uterine blood flow while supine, these researchers also documented a concomitant decrease in the uterine artery luminal diameter. This unexpected finding suggests that the uterine vasculature may be more vasoreactive than previously assumed. During supine exercise (e.g., stomach crunches and leg lifts), uterine blood flow increased to a level not significantly different from that resulting from the left lateral position. These results suggest that the proscription against supine exercise in pregnancy may need to be reconsidered.

In another study, this same team examined the placentae of a group of women who engaged in frequent moderate- to high-intensity running throughout pregnancy, and a group of pregnant women who were physically active, but who did not participate in regular weight-bearing

exercise. They found that regular running was associated with increased cellular proliferation and increased villous vascular volume in the placenta. Avenues for further research include study of the mechanisms by which regular weight-bearing exercise stimulates placental growth, and whether an exercise regimen could be of benefit for preventing or treating anomalous fetoplacental growth.

Pregnancy and Subsequent Health

A growing body of evidence indicates that women who experience preeclampsia during pregnancy are at increased risk for cardiovascular disease later in life. Preeclampsia may arise in women who have underlying cardiovascular risk factors, such as insulin resistance and chronic inflammation, that are unmasked by the physiological stress of pregnancy, and that persist after delivery. Other pathophysiologic mechanisms involved in preeclampsia and potential targets for prevention and therapy are under active pursuit by PPB-funded investigators. Earlier work indicated that a majority of preeclamptic women experienced an abnormal immune response, called autoimmunity, in which their bodies produced antibodies against one of their own proteins; these antibodies are called autoantibodies. Autoantibodies target a receptor, designated AT-1, that is involved in mediating the effects of Ang II, described earlier and involved in the contraction of blood vessels. In contrast to most antibodies that neutralize their targets, autoantibodies actually activate AT-1 receptors. Researchers speculate that these autoantibodies are responsible for the hypertension associated with preeclampsia because of the ability of these substances to contract blood vessels.

Agonistic Ang II type-1 receptor autoantibodies (AT1-AA) have been detected in women with preeclampsia and may contribute to the syndrome through activation of the Ang II type-I receptor, causing vasoconstriction and hypertension. It is not clear whether these autoantibodies remain in the maternal system after delivery, or whether they contribute to later cardiovascular risk. A PPB-funded group of researchers examined serum levels of AT1-AA and other factors at 18 months postpartum in women who had preeclampsia and in women who had normal pregnancies. AT1-AA were present in a significantly higher proportion of women who had a history of preeclampsia than in normal controls. Women with autoantibodies had higher sFlt-1 levels, lower VEGF levels, and higher insulin resistance compared to women without autoantibodies. AT1-AA have already been linked to a variety of cardiovascular conditions, meaning they may also be a marker for future development of cardiovascular disease in women who had preeclampsia.

Microchimerism refers to the presence of two distinct cell populations, originating from two different individuals, that co-exist in a single person. Fetal cell microchimerism arises from the transfer of fetal cells into the maternal circulation during pregnancy. This transfer occurs in all pregnancies, and fetal cells are known to persist in maternal blood and tissues for many years. A number of studies have implicated fetal microchimeric cells as factors related to later autoimmune illness, such as systemic sclerosis, in parous women. Recent evidence, however, indicates that fetal microchimeric cells have the potential to differentiate into hepatic, epithelial, and leukocyte phenotypes, meaning they may be involved in maternal tissue repair. To explore potential beneficial effects of fetal microchimerism, a PPB-funded investigator assessed the presence and quantity of fetal cells in the maternal livers of parous mice exposed to chemical or surgical hepatic injury and of control animals. Polymerase Chain Reaction (PCR) results showed

that, after chemically induced hepatic injury, but not after surgically induced hepatic injury, fetal cells were detectable in the maternal liver and spleen, and that the number of fetal cells increased significantly over time post-injury. These findings suggest a novel role for fetal microchimeric cells in maternal health, with possible dynamic involvement in injury type-specific tissue repair. Further studies to assess the fetal cells' phenotype, whether they migrate to the site of injury or proliferate locally, and whether they improve tissue recovery and function are warranted.

Mood Disorders in Pregnancy and Postpartum

Peripartum mood disorders are common and cause substantial morbidity in women, their infants, and families. Depression affects approximately 10 percent to 15 percent of pregnant women. A history of antenatal depression increases the risk of postpartum depression, which also affects 10 percent to 15 percent of women postpartum. The treatment of antenatal depression is challenging because it is not yet clear how best to balance antidepressant medication and untreated depression in terms of risk to mother and infant. A PPB-funded researcher conducted a prospective study of groups of pregnant women, with mild to moderate depression, who were or were not using antidepressants compared to a group of healthy controls. Women using antidepressants were significantly more likely to experience preterm birth and had a lower mean gestational age at delivery (GAD) than women with untreated depression and than normal controls. There seemed to be an inverse relationship between dose of antidepressant and GAD. There was no difference in GAD or preterm birth rate between untreated women and healthy controls. Though questions still remain, this study provides important information for clinicians to consider when counseling pregnant women who have depression.

Obesity is a well-described risk factor for depression. Given the dramatic rise of obesity among women of childbearing age, could an epidemic of perinatal mood disorders also be developing? To address this question, one PPB-funded investigator conducted a population-based study of the relationship between self-reported prepregnancy body mass index (BMI) and depressive symptoms in a cohort of women at two months to four months postpartum. Moderate or greater depressive symptoms were more commonly reported by women at the extremes of BMI, i.e., those who were underweight (BMI < 19.8) or obese (BMI > 29). This preliminary work suggests that further research into the possible association between postpartum depression and extremes of BMI is warranted.

Mechanisms of Abnormal Placentation

Preeclampsia is thought to result from abnormal placental development early in pregnancy. Better understanding of the mechanisms of early placental development may lead to novel preventive or therapeutic measures for preeclampsia and other placental disorders. Under normal conditions, specialized cells of the placenta (called cytotrophoblasts) aggressively invade the uterus to graft the embryo onto the maternal blood supply. This process is more akin to tumorigenesis than to organogenesis. The invasive property of the cytotrophoblast is normally limited and, once the maternal-fetal blood supply is established, the cytotrophoblasts differentiates to a non-invasive cell type. The mechanism by which this switch from an invasive to non-invasive cell type occurs is unknown. PPB-funded researchers have shed light on this important process. They demonstrated that the switch from an invasive to non-invasive cell type is associated with aneuploidy, specifically an increased number of specific chromosomes. Aneuploidy also correlated to reduced cell proliferation. This finding is a conundrum because

aneuploidy is a condition in which the chromosome number of a cell is abnormal and is generally a characteristic of an abnormal or tumor cell. The researchers speculate that aberrations in chromosome number are a normal part of cytotrophoblast differentiation, rather than an anomaly, and that these aberrations limit the cells' invasive and proliferative potential. This finding may be a plausible mechanism for holding these fetal cells with tumor-like properties in check. In addition, abnormalities in this process may be associated with a number of pregnancy disorders due, in part, to either poor cytotrophoblast invasion (i.e., fetal growth restriction and preeclampsia) or excessive invasion (i.e., placental increta and percreta).

Another PPB-funded team has also been studying the mechanisms underlying abnormal placental development and impaired trophoblast invasion. This investigative team hypothesized that viral infections of the placenta induce pathological changes, which impair trophoblast invasion into the uterine wall, resulting in adverse pregnancy outcomes due to placental dysfunction. Generally, approximately 40 percent to 80 percent of adults are infected with the adeno-associated virus-2 (AAV-2). In earlier work, the investigators used detection of AAV-2 IgG antibodies to determine that approximately 83 percent of pregnant women had been previously infected by AAV-2; however, previous exposure to AAV-2 before pregnancy was not associated with poor pregnancy outcome. In contrast, active infection during pregnancy, either due to a first exposure or to activation of the virus from a previous infection, was associated with severe preeclampsia and other adverse pregnancy outcomes.

Extending this work, the research team recently demonstrated that trophoblast cells *in vitro* can be easily infected with AAV-2, resulting in an inhibition of their invasive properties. Furthermore, AAV-2 DNA was found five-times (55 percent) more frequently in trophoblast cells from the placentas of women who had severe preeclampsia than in those of normal women (18 percent). These results indicate that a common virus is associated with a frequently observed poor pregnancy outcome, and that its mechanism of action targets the trophoblast cells of the placenta to cause impaired trophoblast function. This research suggests that viral infection may play a more significant role in poor pregnancy outcomes than previously recognized. Additional research is warranted to determine the susceptibility of the placenta to other types of common viral infections and their effects on pregnancy outcome.

FETAL RESEARCH

Prenatal Diagnosis

Fetal research, including prenatal diagnosis, remains a key area of interest for the PPB and its supported researchers. The recent explosion in high-throughput genotyping technologies may offer important advances in prenatal diagnostics. However, current microarrays used for many clinical conditions, such as cancer, are too expansive for prenatal testing. Recent work has shown that significant genomic variations, including relatively large deletions, are common between normal individuals; therefore, only microarrays crafted to minimize incorrect or uninterpretable results, yet capable of maximizing identification of clinically relevant mutations will be acceptable for accurate prenatal testing. Studies will also require analyses of large numbers of pregnancy samples to not only confirm diagnostic equivalency to cytogenetic testing, but also to develop sufficient knowledge of the clinical significance of additional findings

resulting from a given method. Although researchers have conducted preliminary studies using novel diagnostic methods on children who have clinical conditions suspicious for a microdeletion, these studies typically have not addressed the unique questions raised in relation to prenatal testing. These and other issues need to be addressed before any new diagnostic method is incorporated into regular practice.

One PPB-supported study is exploring the accuracy and efficacy of Comparative Genomic Hybridization Microarrays (CGH-MA) compared to the present clinical standard of prenatal cytogenetic diagnosis. This study will evaluate the use of CGH-MA on a cohort of pregnancies with abnormal pregnancy outcomes, such as congenital anomalies, stillbirth, growth restriction, or repeat miscarriages. It is likely that CGH-MA may identify subtle small deletions, insertions, or duplications, which could eventually lead to knowledge about the origins of these conditions and facilitate future counseling. Successful demonstration of the accuracy of CGH-MA in prenatal diagnosis could also allow for its routine use in clinical care and could significantly increase access to the technology by all pregnant women. CGH-MA also has un-assessed potential for revealing common changes in the genome that do not have clinical significance, but that if not completely evaluated, could result in incorrect or false-positive diagnoses and patient anxiety. It is important, then, to determine the appropriate application of the method and the genetic counseling that should accompany it before making it standard practice.

Fetal Origins of Adult Diseases

A significant portion of the PPB portfolio deals with research in the area of the fetal origins of adult diseases. Much of this research stems from the early epidemiological work of Barker that showed a relationship between low birth weight and the development cardiovascular disease. During the last decade, this research area has burgeoned; substantial epidemiological and animal-based research has not only supported the original concept, but has also expanded it. Currently, research posits that an inadequate prenatal environment, leading to either a low birth weight, (e.g., due to poor maternal nutrition, placental insufficiency or dysfunction), high birth weight (e.g., due to gestational diabetes), or fetal stressors (e.g., resulting in elevated fetal cortisol production), may permanently alter and program the fetus for the onset of many diseases later in life. The diseases associated with this process are broad and include hypertension, diabetes, cardiovascular disease, and obesity, as well as psychiatric and behavioral disorders. The gross phenomena are well documented; the challenge now is to understand the molecular mechanisms behind the processes of fetal programming. Although it is not possible to describe all the work of PPB-supported investigators in this area due to space limitations, the following section highlights some of these efforts.

One research team studied the effect of administering antenatal glucocorticoids on offspring development of hypertension in adulthood. Using a sheep model, pregnant ewes at 80 days (0.6 gestational interval) of gestation were treated for two consecutive days with betamethasone or placebo. Fetal kidneys were analyzed at 81 days and 135 days (0.9 gestational interval) of gestation. The investigators showed that certain key renal regulatory molecules were acutely and chronically affected following betamethasone treatment. At day 81 of gestation, the levels of Na/H exchanger 3 (NHE3) were increased, levels of Ang II receptor (AT2R) were decreased, and there was no change in the Na, K-ATPase pump (NKAP), angiotensin 1 receptor (AT1R), or type 1 dopamine receptor (T1DR). At day 135 of gestation, levels of AT2R remained decreased,

but T1DR was increased, and there was no change in the levels of NKAP, NHE3, or AT1R. In addition, at 135 days of gestation, the kidneys of fetuses exposed to betamethasone had a 26-percent decrease in the number of glomeruli but no difference in kidney weight. In betamethasone-treated young adults at six months of age, the mean systolic and diastolic blood pressures were significantly elevated compared to non-treated young adults, but there was no significant difference in heart rate. These results suggest that even a transitory increase in the glucocorticoid exposure levels in the fetus can have long-lasting effects and can lead to hypertension in adulthood. Thus, fetuses exposed to stressors that increase the fetal production of cortisol may also be at higher risk for adult-onset hypertension. These results may also have important implications for human neonates who are exposed to antenatal steroids as a way to accelerate fetal lung maturity prior to delivery.

Another PPB-supported team used a non-human primate model to study the effect of maternal nutrient restriction in early gestation on the fetal kidney. Pregnant baboons were nutrient restricted by feeding them 70 percent of their normal diet on a weight-adjusted basis from 30 days (0.2 gestational interval) through 90 days (0.5 gestational interval) of gestation. At 90 days, researchers collected fetal kidneys and conducted global mRNA expression analysis and histology. Findings indicated that nutrient restriction resulted in a down-regulation of genes in pathways related to RNA, DNA, and protein biosynthesis, metabolism, and catabolism. In contrast, genes in cell signal transduction, communication, and transport pathways were up-regulated. Histology indicated decreased tubule density within the kidney cortices of nutrient-restricted fetuses. Because glomerular cross-sectioning per unit area was unaffected by nutrient restriction, it could be that tubule tortuosity and/or tubule length was decreased. Taken together, the changes indicated that nutrient restriction results in accelerated fetal renal differentiation, thus shortening critical phases of renal growth. This shortening may lead to decreased functional capacity of the kidney, resulting in hypertension later in life.

A Branch-funded investigative team studied the effect of nutrient restriction on fetal heart development. Using a sheep model, researchers studied placental insufficiency caused by umbilicoplacental embolization (UPE). After undergoing UPE at 115 days of gestation (0.8 gestational interval), instrumented fetal sheep were weighed and measured 10 days and 20 days later. UPE-treated fetuses weighed less (10 days = -20 percent; 20 days = -27 percent) than control fetuses, but their heart dimensions and weight were appropriate for their reduced weights. Results indicated that 10 days of UPE did not significantly alter the proportion of binucleated myocytes or cell-cycle activity in either ventricle. In contrast, 20 days of UPE treatment resulted in a 16-percent decrease in the proportion of binucleated myocytes in both ventricles and reduced cell cycle activity in both ventricles by 70 percent. These findings are indicative of a less mature myocardium, which may lead to cardiac problems later in life.

Fetal Growth

Normal fetal growth requires the fetus to effectively interface with maternal circulation to ensure that it receives an adequate supply of nutrients and to maintain the proper exchange of gases and waste products. This interface occurs at the level of the placenta. Perturbed or abnormal placental development is associated with a number of serious pregnancy conditions, such as miscarriage, fetal growth restriction, and preeclampsia. One PPB-supported investigative team studied the role of a specific gene during pregnancy within the context of fetal growth. The gene

codes for a protein called adrenomedullin, whose function in pregnancy was poorly understood. The blood level of this protein increases to very high levels during pregnancy; in the last trimester, the level is 500 percent higher than in the non-pregnant state. To learn more about the protein's function, the investigators genetically engineered mice to have only one copy of the gene and mated them to one another or to normal mice, which have two copies of the gene. The genetically engineered pregnant female mice with only one copy of the gene had more placental defects and growth-restricted fetuses than did normal mice. Fetuses lacking all copies of the adrenomedullin gene were more severely affected. These results indicate that adrenomedullin plays an important role in pregnancy, and that maternal-derived and fetal-derived adrenomedullin are both important for normal placental development and the proper growth of the fetus. This research suggests that lower levels of adrenomedullin gene expression can adversely impact pregnancy. Identifying individuals with such defects before pregnancy and treating them during pregnancy with potential therapies to restore normal adrenomedullin levels could be beneficial.

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity, death, and long-term complications, such as diabetes and hypertension in adulthood. IUGR often arises in a setting of uteroplacental insufficiency, a situation in which inadequate oxygen delivery results in chronic fetal hypoxia. A PPB-supported investigative team is examining hypoxia's influence on key fetal growth factors and on gene expression. For example, the action of insulin-like growth factor 1 (IGF-1), a major growth promoter in fetal tissues, is blocked by binding to insulin-like growth factor binding protein 1 (IGFBP-1). Using an animal model, this team showed that exposure to chronic hypoxia significantly increased fetal IGFBP-1 expression, which may directly impair fetal growth, or may block growth by inhibiting the action of IGF-1. Studies of time-dependent fetal-tissue gene expression revealed that hypoxia results in tissue-specific alterations that differ by the duration of hypoxic exposure. For instance, growth-related genes were consistently suppressed, regardless of hypoxia duration, and genes involved in glycolysis, calcium homeostasis, and inflammation were induced by hypoxia of varying duration. Understanding the mechanisms by which hypoxia produces growth failure is key to development of interventions to prevent or treat IUGR.

Prenatal diagnosis of fetal hematologic and genetic disorders offers the opportunity for therapeutic intervention before birth. *In utero* hematopoietic-cell transplantation (IUHCT) refers to the introduction of hematopoietic stem cells into the fetus, ideally serving as a donor tissue graft or inducing donor-specific tolerance to facilitate postnatal cellular and organ transplantation. Consistent and high-level donor-cell engraftment in such cases is often hampered by host-cell competition and dominance in hematopoietic tissues. Researchers supported by the PPB are investigating mechanisms by which donor cells could be given a competitive advantage over host cells and, thus, establish longer-term engraftment. Using a mouse model, the research team is focusing on the process by which donor cells home in on fetal hematopoietic tissues. This research focuses on CD26, a membrane-bound exopeptidase expressed on some hematopoietic stem cells and progenitor cells, which impair donor-cell homing by cleaving a chemokine (SDF-1α) involved in attracting circulating donor cells to the bone marrow cavity. By injecting donor cells, in which CD26 activity was inhibited, into recipient animals, researchers not only significantly increased donor-cell homing, but also significantly enhanced donor-cell engraftment and establishment of macrochimerism. This study

demonstrates that the goal of establishing longer-term hematopoietic allografts during fetal life may be addressed by improving donor cells' ability to home in on host hematopoietic tissues.

LABOR AND DELIVERY RESEARCH

Labor is a complex and interwoven physiological process involving fetal, placental, and maternal signals. A number of stimulatory and inhibitory mechanisms that play different roles in uterine contractility, fetal membrane integrity, and cervical maturation have been identified. The Branch promotes studies of the physiology, endocrinology, and management of preterm, term, and post-term deliveries.

Understanding the normal physiological and biochemical events that occur during parturition is essential for successful interventions for and prevention of preterm labor. Preterm births are increasing in the United States and occur in more than 12 percent of all births, accounting for more than 75 percent of all perinatal morbidity and mortality. Excluding congenital malformations, preterm birth accounts for approximately 70 percent of all neonatal deaths and nearly 50 percent of long-term neurological problems. These long-term neurological problems include serious physical and mental disabilities, such as cerebral palsy, intellectual and developmental disabilities, and vision and hearing loss. Delaying a very preterm birth even by days or weeks has profound effects on reducing neonatal mortality and morbidity. The PPB and the NICHD have made significant research investments in understanding the causes and mechanisms that underlie preterm labor and delivery. The brief descriptions below highlight some findings from PPB-funded efforts related to labor and delivery, including preterm labor and delivery.

One of the prerequisites for a successful birth is that the newborn be able to breathe on its own following delivery. The ability to breathe is critically dependent on the production of surfactant—a mixture of proteins and lipids that prevents the lungs from collapsing during normal breathing—by the lungs. During the last trimester of pregnancy, surfactant production is initiated by the fetal lungs and reaches maximal levels just before birth. Hence, it would make sense that the ability to breathe and the timing of birth would be coordinated, although no evidence has demonstrated such a relationship. A PPB-supported researcher has shown, however, that a surfactant protein, SP-A, may be involved in the timing of delivery. Using a mouse model of parturition, the researcher demonstrated that increasing levels of SP-A, secreted by the fetal lung into the amniotic fluid, induce an inflammatory response in the uterus by activating macrophages present in the amniotic fluid. The activated macrophages migrate to the uterine wall, where they produce inflammatory cytokine interleukin-1, which activates a transcription factor, called nuclear factor-kappa beta (NF-kB), in uterine muscle cells. The activation of NF-kB turns on a molecular cascade, resulting in increased uterine contractility and parturition.

Further research also indicated a role for SP-A in mediating parturition; compelling evidence suggested that the injection of SP-A into the amniotic fluid induces preterm delivery, and that the injection of an SP-A neutralizing antibody delays delivery. The discovery that SP-A secreted by the fetal lung can act as a signal for the initiation of parturition serves as a valuable paradigm

illustrating the intricate relationship between the maturation of the fetus and the timing of delivery. Thus, the fetus can signal the uterus to indicate that its lungs are sufficiently mature to switch from an aqueous to an air environment. Blocking or reversing this signal, then, may be a way to delay parturition, even after the process has begun.

During 95 percent of human pregnancy, the uterus is maintained in a state of almost complete quiescence by elevated levels of circulating progesterone. Myometrial levels of the progesterone receptor (PR) remain elevated throughout pregnancy and into labor. Spontaneous labor, then, is likely mediated by a concerted series of biochemical events that negatively impacts the ability of PR to regulate target genes, which maintain myometrial quiescence. One investigative team has been actively studying the molecular mechanisms involved in this process. They hypothesized that progesterone/PR inhibits uterine contractility by blocking NF-kB and the induction of cyclooxygenase-2, a contractile gene that is up-regulated during labor. The investigators identified a novel role for PR as a potent anti-inflammatory factor in the myometrium. They found that progesterone acts through PR to play a major anti-inflammatory role in human myometrial cells by antagonism of NF-kB activation and the subsequent induction of COX-2, the crucial and rate-determining enzyme in prostaglandin biosynthesis. Because prostaglandins play a critical role for inducing myometrial contractions, prostaglandin activity likely underlies the action of progesterone/PR to maintain myometrial quiescence throughout pregnancy.

Research to understand preterm birth, which accounts for approximately 500,000 births annually, is ongoing. Approximately 50 percent of preterm births occur spontaneously following the premature onset of labor. In addition, many pregnant women experience false preterm labor, i.e., preterm contractions that do not result in a preterm delivery. An effective screening method to determine which women are in spontaneous preterm labor and which ones are simply having preterm contractions would allow clinicians to start necessary treatment for those having true preterm labor and to avoid unnecessary treatment and hospitalizations for those who are not. To develop such a screening method, one PPB-supported investigative team used uterine electromyography (EMG), placement of electrodes on the abdomens, to measure the uterine activity of women in preterm labor, in term labor, and not in labor. The researchers then used an artificial intelligence neural-network computer program to analyze the data and classify the various groups based on their EMGs. This method correctly differentiated more than 90 percent of the women in preterm labor from those in labor at term and from those not in labor. This non-invasive method may provide clinicians with a new tool for properly treating women who are in labor and women who are not.

Approximately 10 percent of preterm births occur because of preterm premature rupture of membranes (pPROM), which leads to either a spontaneous or medically induced delivery. In addition, African American women have a two-fold increase in the risk of pPROM compared to Caucasians. A PPB-supported investigative team studied whether genetic differences between the two groups could account for this health disparity. Using a candidate-gene approach, researchers previously showed that certain single nucleotide polymorphisms (SNPs) increase the promoter activity of genes encoding matrix metalloproteinases, enzymes which break down collagen; this increased activity is associated with an increase risk of pPROM in African Americans. Using a similar approach, the team hypothesized that a particular SNP at position -656 in the promoter of the *SERPINH1* gene, which codes for a chaperone protein essential for

collagen synthesis, may be associated with an increased rate of pPROM in African Americans because the polymorphism is more common in people of African descent. The research confirmed that the -656 T minor allele, compared to the -656 C major allele, is 2.7 times to 5.8 times more common in certain African populations than in Western European Caucasians. In African Americans, the -656 T allele was increased by 1.7 times compared to European Americans. Using functional genetic-construct studies of amnion fibroblasts, the same group also demonstrated that the -656 T allele construct had much less promoter activity than the major -656 C allele construct. Furthermore, the -656 T allele was increased three fold in African American neonates born from pregnancies complicated by pPROM compared to controls. Together, these results suggest that differences in allele frequencies between populations may be responsible, in part, for the health disparity observed in the incidence of pPROM.

Most of the infant mortality and morbidity of preterm birth is associated with the 1 percent to 2 percent of infants born extremely preterm (birth at less than 32 weeks of gestation). A significant percentage of preterm births that occur less than 32 weeks of gestation are associated with infection. Unfortunately, tocolysis or antibiotic treatments are ineffective for preventing or significantly delaying delivery in these cases. Using a non-human primate model (rhesus macaque), a PPB-supported investigative team has focused on this problem. They have shown that antibiotic treatment before the onset of uterine contractile activity eliminated group B streptococcus (GBS)-induced infection, prevented elevations of inflammatory mediators (IL-1beta, -6, and -8; TNF-alpha; prostaglandins), and prevented preterm delivery. Antibiotic treatment given after the onset of uterine contractions eliminated the infection; however, it prevented neither the elevations of inflammatory mediators nor preterm delivery. These results indicate that, once inflammatory mediators are elevated by infection and reach a threshold, the inflammatory process can no longer be reversed by antibiotic treatment alone.

The investigators then hypothesized that a combination of both antibiotics and anti-inflammatory agents may be effective in preventing or at least significantly delaying an infection-induced preterm delivery. As a proof of principle to test the hypothesis, a small number of pregnant rhesus monkeys were inoculated with GBS to induce uterine contractions; monkeys then received no treatment, were treated with antibiotic (ampicillin) alone, or were treated with antibiotic in combination with anti-inflammatory agents (dexamethasone and indomethacin). The mean interval from contraction onset to delivery was 1.4 days in the untreated group, 3.4 days in the antibiotic-treated group, and 8.9 days in the antibiotic/anti-inflammatory-treated group. As expected, antibiotic and anti-inflammatory agent treatment significantly suppressed the level of inflammatory mediators in the amniotic fluid compared to either the control or antibiotic group. Therefore, antibiotic treatment, in combination with anti-inflammatory agents, may be a useful intervention to prevent infection-induced preterm labor. More research is clearly warranted in this promising area.

Reproductive epidemiology—specifically research on the rising rates of cesarean section deliveries in the United States—has also been a focus of PPB-funded researchers. Despite the Healthy People 2010 goal of decreasing cesarean births, the cesarean delivery rate in the United States has risen steadily since 1996, reaching an all-time high (more than 30 percent) in 2005. A major driving force behind the increase in cesarean births is the declining rate of vaginal birth after cesarean (VBAC). In 1996, delivery by VBAC peaked at 28.3 percent; by 2004, VBAC

rates had dropped to 9.2 percent. PPB-supported researchers have studied the safety of VBAC, which is associated with risks of uterine rupture, need for hysterectomy or transfusion, and endometritis. Investigators reviewed more than 25,000 records from women who had prior cesarean deliveries; the data included women served by tertiary and community hospitals and at facilities with and without obstetrics/gynecology residency programs, making the results more generalizable to a wider spectrum of obstetric patients. Data showed that the incidence of uterine rupture among women who had a prior cesarean and who attempted VBAC was less than 1 percent; this figure is important because some have suggested that the occurrence of uterine rupture is on the rise in the United States. Researchers also found that a prior vaginal delivery was associated with a 60-percent reduction in the likelihood of rupture. However, uterine rupture in those attempting VBAC delivery, in general, could not be accurately predicted. This large, generalizable, observational study of maternal VBAC safety found that the overall incidence of uterine rupture in those attempting VBAC was quite low, less than 1 percent in 2000. The investigators concluded that women who had a prior cesarean should be offered VBAC, and that women with a prior cesarean and prior vaginal delivery should be encouraged to use VBAC.

The Branch also funds a diverse portfolio on the circumstances of parturition, with projects that use physiological, biochemical, and molecular approaches to elucidate the various mechanisms involved, including (but not limited to): the role of the hypothalamic-pituitary-adrenal axis in both preterm and term labor; the involvement of hormones such as corticotropin-releasing hormone, adrenocorticotrophic hormone, cortisol, and androgens in parturition; mechanisms, such as infection, cytokine production, and extracellular matrix biology, involved in pPROM; and uterine relaxation and contraction factors, such as nitric oxide (NO), oxytocin, relaxin, steroids, and prostaglandins, and their mechanisms of action. This research will provide a better understanding of the mechanisms responsible for parturition to help promote successful labor and deliveries. In addition, the clinical, translational, and epidemiological research funded by the Branch augments its basic science research in the development of preventive and therapeutic measures necessary to optimize pregnancy outcomes.

NEONATAL RESEARCH

The Branch supports basic and clinical studies concerned with the etiology, pathophysiology, therapy, and followup of conditions associated with the perinatal and neonatal period; these include adaptation to extrauterine life, hyperbilirubinemia, and sequelae of preterm birth, such as asphyxia, respiratory distress, bronchopulmonary dysplasia, hypoglycemia, anemia, and infection. In addition to the PPB, other NICHD Branches and NIH Institutes support neonatal research. Funded projects share the common aim of clarifying neonatal physiology and pathology to permit further developments in the care of these infants. Results from some Branch-supported activities are described below.

Estrogen Receptors and Endothelial Cells

New blood vessel development in the ovary, uterus, and placenta is regulated by estradiol-17β (E2) acting through estrogen receptor α (ERα). The underlying processes include direct actions of E2 on endothelial cells to promote growth and migration. These mechanisms also mediate cardiovascular protection by E2 for many years after the childbearing age. Investigators funded by the NICHD have shown that E2 stimulates endothelial NO synthase via the activation of plasma membrane-associated ERα, and that the non-genomic function of these receptors entails G-protein coupling. Using pull-down experiments with purified recombinant proteins, the investigators demonstrated that ERα binds directly to Gαi and Gβγ. Mutagenesis and the addition of blocking peptide revealed that this binding occurs via amino acids 251–260 and 271–595 of ERα, respectively. Through direct interactions, ERα mediates a novel mechanism of G-protein activation that provides greater diversity of function for both the steroid hormone receptor and G proteins. This work enables researchers to segregate genomic and non-genomic estrogen action, with the ultimate goal of harnessing the non-genomic mechanisms for cardiovascular benefit without perturbing oncogenic processes.

Hypoxia/Asphyxia in the Fetus and Newborn

The Branch supports a number of research teams studying hypoxia/asphyxia, namely in trying to understand the mechanisms of the condition, its causes, and its effects on the outcomes of infants. Some of this research includes the following:

- Researchers in the White Mountains of California found that the cerebral vascular tone of the fetus goes through a spectrum of acclimatization changes, including increased media thickness due to increases in smooth muscle cell layers, marked increase in the size of perivascular nerves, and a number of pharmaco-mechanical couplings, in response to long-term hypoxia (LTH). Results from this and other research suggest that in the fetus, LTH is associated with decreased vascular tone, which may play a key role in optimizing cerebral blood flow under hypoxic conditions. LTH seems to accelerate maturation of many fetal cerebrovascular mechanisms and serves to illustrate the concept of "developmental plasticity"—that is, a fetus that matures more quickly enhances the chances for survival for both mother and fetus. From a teleological point of view, these changes serve to optimize cerebral blood flow and, thus, O_2 delivery in the face of decreased O_2 levels.
- Researchers are working to understand the mechanisms of long-term effects of stress during pregnancy, and of fetal low birth weight, on disease in the adult. Using ovine placentomes, researchers demonstrated that LTH from high altitude was associated with an approximately 40-percent increase in capillary density and caused significant changes in ovine placentome. The same team also noted that a number of genes in the mouse placenta were up- or down-regulated in response to 48 hours of hypoxic stress (from embryonic day 15.5 to day 17.5). In response to maternal protein deprivation (50-percent protein with normal calories, vitamins, and minerals), another subset of genes were up- or down-regulated. For the most part, the stress-induced gene-expression changes were unique to each state, hypoxia or protein deprivation.
- A large body of Branch-supported research has produced several basic discoveries to explain the mechanisms of neuronal cellular death due to asphyxia in the newborn period. These findings offer an opportunity to intercept the cell-death pathway and facilitate the development of strategies to prevent or attenuate neuronal injury. For example, one research

- Research is also striving to understand the basic processes involved in the etiology of hypoxia-mediated pulmonary hypertension in newborn infants. For instance, endothelin-1 (ET-1) mediates hypoxia-mediated pulmonary vascular remodeling (HPVR), and an endothelin-A receptor (ET-AR) blockade prevents HPVR in newborn mice. Researchers determined the postnatal effects of chronic hypoxia and/or ET-AR blockade on lung ET-1, ET-AR, endothelin-B receptor, and vascular collagen and elastin. By exposing newborn C57BL/6 mice to air or hypoxia (12-percent oxygen) from birth for 1 day, 3 days, or 14 days, and then assessing vascular collagen, elastin, and endothelin, investigators found that:
  - Hypoxia attenuated the normal postnatal decrease in ET-1 and collagen content.
  - The ET-AR blockade reduced collagen independent of oxygen.
  - Hypoxia increased elastin mRNA expression and attenuated the normal postnatal decrease in elastin content.
  - BQ610 reduced elastin mRNA but not elastin content.

Cerebrovascular Smooth Muscle Maturation and Contractility

- Blood vessels are conglomerates of many different cell types in continuously varying stages of maturation. NICHD-funded researchers studied the contractility and the distribution of multiple markers of smooth-muscle phenotype in the carotid and cerebral arteries of developing animals. This work revealed that, as arteries mature during the postnatal period, their expression of synthetic markers (such as non-muscle myosin) is gradually supplanted by increased expression of contractile proteins (such as the SM2 isoform of myosin). These and other findings indicated that contractility is regulated through fundamentally different mechanisms in fetal and adult cerebral arteries. The overall contribution of this research provides a basis to better understand maturational aspects of cerebral vasculature, as well as to begin to study mechanisms of ischemic damage to the blood vessels through the lifespan.

Lung Development

As mentioned earlier, one of the prerequisites for a successful birth is that the newborn be able to breathe on its own following delivery. The following are findings from PPB-supported research on lung-related topics of the newborn:

- To understand the mechanisms of persistent pulmonary hypertension (PPHN) in newborns, researchers showed that the increase in pulmonary blood flow that normally occurs at birth is related to an increase in synthesis and release of adenosine triphosphate (ATP), which is released in response to increased postnatal oxygen concentrations. They also found that increased ATP acted as a signal to increase pulmonary blood flow. Normally, ATP interacts with nitric oxide synthase (NOS) to stimulate NO release into the pulmonary circulation; in models of PPHN, however, this mechanism is altered so that other enzymes (not NOS) were

involved in the release of superoxide, a vasoconstrictor. These findings may assist future development of therapeutic agents, which could help correct the imbalance in NOS function.

- To define the phenotype of congenital alveolar capillary dysplasia (ACD) as a first step toward mapping the responsible gene(s), investigators analyzed pathology reports and microscopic slides of 23 subjects with ACD and conducted sequence analyses of two candidate genes. The investigators delineated the natural history of ACD and its associated anomalies and corroborated the likely autosomal recessive nature of this condition in some families. Using sequence analysis, the investigators were able to exclude mutations in the coding region of two candidate genes, bone morphogenetic protein type II receptor (*BMPR2*) and endothelial monocyte-activating polypeptide II (*EMAP II*), as candidates for ACD.
- One unique PPB-supported study is developing a step-by-step approach to resuscitation in an animal model (fetal/neonatal lambs), enabling testing and fine tuning of methods to determine which approach is least damaging to the lungs. Investigators simulated the actual, real-life method of resuscitating preterm infants in a sheep model and varied the amount of air and oxygen mixture delivered into the lungs with and without keeping the placental circulation intact. Preterm lambs delivered at 129 days of gestation (about 30 weeks' in humans) were resuscitated in a way that simulates the way human babies are typically resuscitated: a tube inserted in the trachea, large volumes of air/oxygen mixture (called hand-bag-ventilation at 15 ml/kg) blown through the tube for 15 minutes, no positive end-expiratory pressure. After the initial 15 minutes, the lambs were given standard intensive care given to babies (surfactant and additional ventilatory support for two hours, 45 minutes). The control group received no resuscitation and was maintained with placental support. Following analysis of lung fluid and other biological specimens, researchers found that within 15 minutes of "routine" method of resuscitation, the lungs were already damaged with inflammatory cells and normal and abnormal protein leakage into the lung spaces. Thus, the current "standard method of ventilation" can initiate an injurious process in the preterm lung.
- Using preterm animal models, a group of PPB-supported researchers is attempting to understand the factors that enhance fetal and neonatal lung injury from inflammatory mediators, in an effort to develop treatment strategies that reduce the burden of chronic lung disease. The researchers induced amniotic fluid inflammation in experimental pregnant sheep using injections of endotoxin and then delivered the lambs on the day 130 of gestation (equivalent to 34 weeks of human pregnancy); lambs were supported by various ventilatory strategies. The results showed that endotoxin-exposed lungs required higher ventilation pressures, although ventilation per se did not increase lung injury. However, the trachea and lungs of the ventilated endotoxin-exposed animals contained six to 12 times more inflammatory cells than controls, indicating that fetal lung inflammation has a very serious effect on the developing immature lungs.
- In a different set of experiments, the same group of investigators sought to determine whether continuous positive airway pressure (CPAP) ventilation minimized lung injury. In preterm lambs delivered at day 133 of gestation and randomized to three groups (e.g., no ventilation, conventional mechanical ventilation, or CPAP), researchers found that the CPAP-treated lambs breathed without distress to maintain normal blood carbon dioxide levels. These findings, when validated in human infants, could help reduce the long-term burden of chronic lung disease.

Neonatal Pain

The Branch supported the following studies on pain and pain control during the neonatal period:

- The Branch funded the NEOPAIN Study, a multi-center, controlled trial of prophylactic, preemptive analgesia in high-risk newborn infants (born at 24 weeks' to 32 weeks' gestation) who were receiving mechanical ventilation support. The findings of this study, published in *The Lancet*, showed that preemptive analgesia markedly reduced pain experience, but it also increased the incidence of adverse side effects. There was a strong correlation between a need for any analgesic support and poor outcome. The study also concluded that continuous infusion of opioid analgesic was associated with more systemic side effects than intermittent use of the same treatment, as clinically needed. The findings of this important study will have a significant impact on clinical practice. The investigators are planning a followup of surviving children from this study.
- In another PPB-supported study, the researchers found links between cumulative exposure to pain in the Neonatal Intensive Care Unit (NICU) and programming of the hypothalamic-pituitary-adrenal (HPA) axis. The findings are important because the end product of the HPA axis—cortisol—is the body's primary stress hormone, important in cognitive functioning, learning, memory, and immune functions. In a mixed cross-sectional and longitudinal study of 225 infants, researchers examined the developmental trajectory of basal salivary cortisol concentrations at three months, six months, eight months, and 18 months corrected age. Infants born at extremely low GA (less than 28 weeks' gestation) showed down-regulation of cortisol levels at three months, then a shift over time to up-regulation from eight to 18 months. This resetting of basal HPA activity, relative to infants born 29 weeks' to 32 weeks' gestation and full-term infants, suggests one possible mechanism for altered neurodevelopment in this vulnerable population.
- The same researchers also found that repeated exposure to neonatal procedural pain among neurodevelopmentally immature preterm infants could contribute to modulation of HPA-axis functions, especially at sites where hormonal responses to pain are processed. Immature infants may be at greater risk for long-term deleterious consequences from cumulative pain exposure. These findings underscore a continued need for studies to develop methods to prevent pain and therapeutic options to treat procedural pain for acutely ill newborn infants.

Neonatal Skin

Because the skin of an infant in the newborn period is very thin and is less acidic compared to adult skin, it becomes an important portal for infections. NICHD-funded researchers have been studying the biology of newborn skin in an effort to enhance its maturation. In one study, they determined the effect of a topical application of group of proteins, called liver X-receptor activators, to see if acidification of skin layers in the neonatal period could be enhanced, thereby reducing functional abnormalities in permeability barriers, homeostasis, and integrity and cohesion of the skin. In the newborn rat model, they found that such topical applications accelerated the acidification of the skin layer and stimulated the formation of an acidic stratum corneum; these changes are deemed to provide a protective buffer against invading bacteria. They also studied the mechanisms by which these processes are governed. This type of research has potential for developing agents to enhance skin-barrier functions in the newborn period to prevent infections acquired through the skin.

Newborn Antiseptic Washing and Neonatal Mortality in Nepal

Investigators funded through the Branch tested the effects of cleansing the newborn baby soon after birth and of umbilical cord care on infection survival rates. Using a community-based cluster randomization design in rural Nepal, researchers recruited 17,299 newborn infants into the skin-cleansing group (cleaned with a dilute antiseptic solution of 0.25-percent chlorhexidine) and 13,724 infants into the cord-care group (cleaned the umbilical cord site with 4-percent chlorhexidine) for 10 days and compared results to those of infants given the standard care, namely, the soap-and-water cleansing and "dry cord care" of the umbilical region. The chlorhexidine skin-cleansing intervention led to a 13-percent reduction in neonatal mortality compared with the standard care group. Among the low birth weight infants in the chlorhexidine skin-cleansing group, there was a 30-percent reduction in neonatal mortality. In the umbilical cord-care arm, there was a 23-percent to 63-percent reduction in the rates of infection at the umbilical cord site in the chlorhexidine care group compared to controls. *The Lancet* editorial strongly endorsed implementing this strategy globally.

Early Breastfeeding and Infant Mortality Risks

Initiation of breastfeeding within one hour after birth has been associated with reduced neonatal mortality in a number of rural communities. However, the time for initiation of breastfeeding is not uniform; in some cultures, mothers, fearing that the colostrum is "unhealthy," do not begin breastfeeding until up to 48 hours after birth. To examine the trends in the time of initiation of breastfeeding and early neonatal outcomes, the investigators who conducted the chlorhexidine study in Nepal (mentioned above) prospectively collected longitudinal data on breastfeeding patterns and infant outcomes in the Nepalese cohort. Based on 22,838 breastfed newborns who survived to 48 hours after birth, they estimated the association between breastfeeding initiation and death. Within one hour of birth, 3.4 percent of infants were breastfed; 56.6 percent were breastfed within 24 hours of birth. Partially breastfed infants (72.6 percent) were at higher mortality risk (RR = 1.77; 95% Confidence Interval [CI] = 1.32-2.39) than those who were exclusively breastfed. Mortality was higher among those who initiated breastfeeding late ($\geq$ 24 hours) compared with those who initiated early (< 24 hours) (RR = 1.41; 95% CI = 1.08-1.86) after adjusting for low birth weight, preterm birth, and other covariates. The authors concluded that between approximately 7.7 percent and 19.1 percent of all neonatal deaths may be avoided with universal initiation of breastfeeding within the first day of life or hour of life, respectively. Although the relevance of these data for the U.S. population needs to be studied, it seems that programs to promote breastfeeding in rural areas need to focus on early initiation, in addition to exclusivity and duration of breastfeeding.

Fetal and Neonatal Environment and Later Health Problems

Prenatal viral infection is associated with development of schizophrenia and autism spectrum disorders (ASDs) later in life. One study funded by the PPB showed that late first-trimester administration (embryonic day [E] 9 or E9) of influenza virus caused deleterious effects on brain structure and function in mouse offspring. The investigators hypothesized that late second-trimester infection (E18) in mice may lead to different patterns of brain gene expression and result in structural defects in the developing offspring. Mice were infected on E18 with a sub-lethal dose of human influenza virus or sham-infected using vehicle solution. Male offspring of the infected mice were collected at postnatal day 0, postnatal day 14, postnatal day 35, and postnatal day 56 (which correspond to human birth, childhood, adolescence, and adulthood,

respectively); the brains were removed and the prefrontal cortex, hippocampus, and cerebellum were dissected and flash frozen. Microarray, qualitative real-time PCR, diffusion-tensor imaging and magnetic resonance imaging (MRI) scanning, western blotting, and neurochemical analysis were performed to detect differences in gene expression and brain atrophy. Expression of several genes associated with schizophrenia or ASDs, including Semaphoring 3A, Transferrin Receptor 2, and Very Low Density Lipoprotein Receptor, were altered, as were protein levels of Forkhead Box P2. Imaging revealed significant atrophy in several brain areas as well as white-matter thinning in the corpus callosum. Neurochemical analysis also revealed significantly altered levels of serotonin (in postnatal day 14 and 35 samples), 5-Hydroxyindoleacetic acid (in postnatal day 14 samples), and taurine (in postnatal day 35 samples). The investigators propose that maternal infection in the mouse provides an heuristic animal model for studying the environmental contributions to the geneses of schizophrenia and ASDs.

In addition, a large body of evidence suggests that adult-onset coronary artery disease, diabetes, and hypertension may have developmental origins. For example, when glucose and other nutrient supplies are deficient in the fetus, the fetus does not grow adequately. Thus, abnormal fetal metabolism of glucose may be related to poor fetal growth, as may be adult-onset diabetes. A number of investigators supported by the Branch are studying fetal insulin production, the size of the pancreatic islet cells, factors affecting fetal growth, and the relation of these factors to later glucose homeostasis. One study addressed how pancreatic cells of fetal sheep responded to changing blood glucose levels. The researchers found that after prolonged hypoglycemia (14 days) followed by recovery to normal blood glucose levels, the fetal insulin response was inherently weaker compared to adult controls, and to those with short-term hypoglycemia. Recovery responses were also less optimal in animals exposed to long-term hypoglycemia. Fetuses subjected to chronic starvation did not respond to glucose infusion by producing insulin, as occurs in a normal fetus. The programming of pancreatic insulin secretion in response to fetal glucose deprivation may be a mechanism for adult-onset (type 2) diabetes, meaning this lack of insulin response may underlie the origin of diabetes in later life.

Bilirubin and Neonatal Jaundice

Glucuronidation and transporter-mediated efflux into bile are important in the elimination of xeno- and endobiotics, including the natural biladienone pigment bilirubin. The mechanisms of these processes and the structural factors dictating whether cholephilic compounds are excreted directly in bile or whether they require prior glucuronidation are poorly understood. To investigate effects of molecular shape and intramolecular hydrogen bonding on the interplay between direct excretion and glucuronidation in the liver, Branch-supported researchers studied a series of novel synthetic exploded and homologated bilirubin analogues. Metabolism studies were done in rats, including Gunn rats, which are congenitally deficient in UGT1 glucuronosyl transferases, and TR- rats, which are deficient in the canalicular transporter Mrp2 (Abcc2). The results showed strikingly that minor, seemingly inconsequential changes in constitution, amplified by their influence on hydrogen bonding and molecular conformation, can profoundly influence competing clearance pathways in the liver, an effect that is unlikely to be restricted to bis-dipyrrinone carboxylic acids. Exposed carboxyl groups seemed to favor the direct route of elimination, whereas the potential for carboxyl infolding by hydrogen bonding seemed to favor glucuronidation. The results also showed that molecular shape is less important than once assumed for the hepatic glucuronidation and biliary excretion of bilirubin.

Level and Volume of Neonatal Intensive Care and Mortality in Very Low Birth Weight (VLBW) Infants

Community hospitals have seen a large increase in both the number of NICUs and the complexity of the cases treated in these units. Investigators examined differences in neonatal mortality among VLBW (< 1,500 g) infants among NICUs of various care levels and with different volumes of VLBW infants. Researchers linked birth certificates, hospital discharge abstracts, and fetal and infant death certificates to assess neonatal rates among 48,237 VLBW infants born in California hospitals between 1991 and 2000. The mortality rates varied according to both the level of care at the delivery hospital and the volume of VLBW patients; compared with high levels of care and a high volume of VLBW infants (more than 100 such deliveries each year), lower levels of care and lower volumes of these patients were associated with higher odds ratios for death, ranging from 1.19 to 2.72 (95% CI = 1.04-3.12). However, fewer than 25 percent of VLBW deliveries occurred in facilities with NICUs that offered a high level of care and had a high volume of these patients. The authors estimated that increased regionalization of NICUs had the potential to prevent 21 percent of deaths among VLBW infants.

Mortality Differentials and Ethnicity

A group of Branch-supported investigators studied health outcomes of neonates in nine subgroups of the U.S. Asian population (e.g., Cambodian, Chinese, Filipino, Indian, Japanese, Korean, Laotian, Thai, and Vietnamese) using a cross-sectional comparison model. Researchers assessed and compared outcomes for births to mothers from these subgroups and from non-Hispanic white mothers for all California births between January 1991 and December 2001. The unadjusted mortality rate for births to non-Hispanic white mothers was 2.0 deaths per 1,000 births. The unadjusted mortality rate for births to Chinese and Japanese mothers was significantly lower (1.2 per 1,000, $P < 0.001$; 1.2 per 1,000, $P = 0.004$, respectively), while the rate for births to Korean mothers was significantly higher (2.7 per 1,000, $P = 0.003$). After adjusting for risk, infants born to Cambodian, Japanese, and Korean mothers had significantly lower neonatal mortality rates compared with infants born to non-Hispanic white mothers (adjusted odds ratios: 0.58 for infants of Cambodian mothers, 0.67 for infants of Japanese mothers, and 0.69 for infants of Korean mothers); infants of Thai mothers had higher neonatal mortality rates (adjusted odds ratio: 1.89; $P < 0.05$). The researchers noted significant variations in neonatal mortality between subgroups of the Asian American population that are not entirely explained by differences in observable risk factors. Efforts to improve clinical care that treats Asian Americans as a single, homogeneous group, then, may miss important opportunities for improving infant health in specific subgroups.

Development of Cytomegalovirus (CMV) Vaccine in Animal Model

Researchers supported by the PPB are working on an experimental vaccine to reduce stillbirths among rodents born to mothers infected with CMV—a common virus that can also cause intellectual and developmental disabilities and hearing loss in newborn children who are infected in early fetal life. Female guinea pigs, given the CMV vaccine before becoming pregnant, gave birth to fewer dead pups and were less likely to transmit the infection to their offspring than were female guinea pigs that did not get the vaccine. The experimental vaccine differs from traditional vaccines, which are made from a whole-killed virus, because it uses an altered virus

(called a vector) to deliver one gene from the viral DNA to the animals' cells. Once injected, the cells begin manufacturing the viral protein. Cells of the guinea pigs' immune system detected the viral protein and launched an attack against it, thus learning to recognize CMV. The gene used in the experimental guinea pig CMV vaccine—*UL83*, also called *pp65*—contains the information needed to make a protein involved in the infection process; the virus used to make the vector vaccine (Venezuelan Equine Encephalitis Virus) was altered to prevent it from reproducing and infecting new hosts.

The young female guinea pigs in the study were vaccinated three times at two-month intervals before they became pregnant and were injected with the guinea pig form of CMV early in their third trimester. Tests showed that rodents given the experimental vaccine had acquired immunity to guinea pig CMV. The vaccinated guinea pigs also showed T-cell activity against the virus, a step critical to the response against disease-causing organisms. Results in the animal model will provide the basis for developing a version of the vector vaccine to possibly test in humans.

Cochrane Neonatal Review Group (CNRG)

The NICHD-funded CNRG conducts systematic reviews of randomized controlled trials in neonatal medicine. The 245 full-length reviews, posted on the NICHD Web site at http://www.nichd.nih.gov/cochrane/default.cfm, make the CNRG second among the 50 Cochrane Review Groups in number of reviews. Unlike the National Library of Medicine's PubMed database system, which provides only abstracts of reviews, the NICHD Cochrane Web site provides full-length papers for download at no cost.

Reviews are performed by experts, who are identified by a group of international editors. The CNRG is also planning to develop and implement training on systematic reviews and in meta-analysis. In addition to the Web site noted above, the CNRG reviews are published in the Cochrane Library, Issue 1, 2008. The CNRG Web page is one of the most frequently visited pages on the NICHD Web site.

SUDDEN INFANT DEATH SYNDROME (SIDS) RESEARCH

The NICHD, led by the PPB, has been the primary federal resource for research on SIDS since the SIDS Act of 1974 was passed. Its efforts have included and still include studies on the causes and etiology of SIDS, ranging from basic research with animal models to more applied methods involving responses to environmental risk factors; research on the incidence and prevalence of SIDS, especially among certain portions of the U.S. population; and outreach designed to educate parents and caregivers about ways to reduce SIDS risk, especially among those populations with a higher incidence of SIDS. The following sections describe some highlights from the PPB's SIDS research portfolio.

Etiology and Pathogenesis

STUDIES OF BRAIN ABNORMALITIES AMONG SIDS INFANTS

Researchers have studied the underlying processes that may lead to SIDS for many years. Recently, investigators reported important findings—a body of work that has resulted from almost 20 years of NICHD- and PPB-supported research—regarding the brains of infants who die of SIDS. Researchers had previously reported that infants who died from SIDS had a unique deficit in a neural network within the medullary raphe of the brainstem; this network uses the neurotransmitter serotonin and controls heart rate, breathing, blood pressure, temperature, and arousal from sleep. By comparing the brains of infants who died from SIDS to those of infants who died from other known causes, researchers found that the serotonin system deficit was more widespread than previously realized. Specifically, researchers found (*JAMA*, 2006; *296*, 2124-2132) that:

- Brainstem tissue from SIDS infants contained more serotonin-using neurons than did the tissue from infants who died from other known causes.
- These serotonin-using neurons from SIDS infants seemed to contain fewer serotonin receptors than did tissue from infants who died of other known causes. Specifically, tissues from SIDS infants had very little of a serotonin receptor known as "Subtype 1A," which inhibits nerve-cell firing when serotonin binds to it.
- Relative to the increased number of serotonin-using neurons in SIDS infants, the tissues had fewer proteins that recycle serotonin than the tissues of infants who died from other known causes, meaning that the infants who died of SIDS had significantly impaired ability to use serotonin.
- Brainstem abnormalities were observed in about three-fourths of SIDS infants.

Researchers are now trying to develop tests to identify infants with these abnormalities at birth, and to improve strategies for preventing death among these infants. To accomplish these goals, researchers need to understand how the abnormalities alter an infant's physiology. If they can understand how these abnormalities develop, researcher may also be able to design interventions to prevent the abnormalities from occurring in the first place.

Although SIDS infants' tissues in the research described above showed more serotonin neurons, the neurons were morphologically immature and functionally abnormal. Such abnormalities are likely to originate in pregnancy, while the fetus is developing *in utero*. To determine when such development might occur, the same group of investigators studied the development of the human medullary 5-HT system, whose neurons are normally distributed throughout the medullary raphe. Using immunocytochemical techniques in animal models, researchers found that the medullary 5-HT system began to form in the embryo, with the raphe primordia appearing as early as seven weeks' gestation; by 20 weeks', the topography of the medullary 5-HT system was in place (*Auton Neurosci*, 2007; *132*, 92-102). These findings provide evidence that early prenatal insults, such as exposure to alcohol or tobacco, could cause abnormalities in the medullary 5-HT system.

The Aberdeen Area Infant Mortality Study (AAIMS), conducted in collaboration with the Aberdeen Area Tribal Chairman's Health Board and was funded by the NICHD, the Indian

Health Service (IHS), and the CDC, sought to understand why the SIDS rates are so high among Northern Plains Indians, who have among the highest SIDS rates in the United States. The study was the first to link epidemiological findings with neurochemical deficits in the developing human brain. Researchers observed that serotonin-receptor binding abnormalities in the brainstem regions of SIDS cases in the AAIMS were similar to those observed in other populations. In addition, among AAIMS infants, the abnormalities in the arcuate nucleus were more frequent if the mother smoked cigarettes and used alcohol during early pregnancy, or before or throughout pregnancy. This finding supports outcomes reported in the previous section that describe the development of the medullary 5-HT system early in fetal growth.

Researchers from the AAIMS collaborated with investigators on another NICHD-funded SIDS study in Northern Plains Indians to report on a unique case that was common to both studies. A Northern Plains Indian baby boy was enrolled in a prospective study, which took measurements of nervous system control of the heart at two days of age; the boy became part of the AAIMS when he died from SIDS at age two weeks. Upon review of the case, researchers discovered that the boy had abnormal regulation of the heart rate during sleep in response to the "tilt test" (described in the previous section) at age two days compared to other infants in the prospective study who lived. At autopsy, the infant's brain showed the same serotonin-receptor abnormalities in the brainstem neural network observed in other SIDS infants in other populations. To the researchers, this case demonstrated that abnormalities in the brainstem common to infants who die from SIDS may be detectable by physiological tests before death. These findings need to be replicated in larger populations to develop predictive screening tools for identifying infants at possible increased risk of SIDS (*J Neuropath Exp Neurol*, 2005; *64*, 689-694).

Another PPB-supported research project is using an animal model to examine the role of serotonin in regulating breathing responses to high levels of carbon dioxide as a way to understand a possible cause of SIDS. Researchers found that if they raised serotonin levels in the medullary raphe, shown in research described above to have serotonin-receptor deficits in SIDS infants, the breathing response to elevated carbon dioxide was increased (*J Appl Physiol*, 2004; *97*, 1763-1773). This finding supports previous findings that serotonin-activated neurons in the medullary raphe may play a role in causing SIDS because of that brain region's involvement in breathing response, body temperature regulation, and arousal.

Other research has shown that some infants who die from SIDS have other brain abnormalities, such as having less myelin—a lipid-rich insulation covering nerve fibers and commonly known as "white matter"—in their brains. Myelination, necessary for normal functioning of the brain, starts in fetal life and continues through the first two years of life. The patterns of under-myelination in SIDS infants suggest a delay in the development of myelin; this situation occurs in other disorders in which the growth of the infant is impaired. To learn more, researchers used animal models to study the outcomes of those periodically deprived of oxygen for short periods of time, and then given oxygen, in an effort to mimic what happens in SIDS infants, who may have breathing problems or who may not respond properly to hypoxia. Results indicated that oxygen-deprived tissue tries to improve its ability to get oxygen by making more blood vessels, but creates less myelin compared to brains never deprived of oxygen. When oxygen was completely returned, the extra blood vessels disappeared, but the myelin never developed to the

extent that it should have. Thus, early short-term hypoxia results in permanent long-term developmental brain injury (*Am J Physiol Regul Integr Comp Physiol*, 2006; *290*, R1105-R1114), a finding that reinforces the importance of identifying infants with breathing problems as early in life as possible.

STUDIES OF ENVIRONMENTAL FACTORS AND SIDS

Other Branch-funded researchers are working to understand how environmental factors might influence autoresuscitation, the failure of which may contribute to SIDS. Some have proposed that stomach sleeping increases the likelihood that the infant, face down in the bedding, will rebreathe expired air low in oxygen (hypoxia) and rich in carbon dioxide. In addition, some theorize that an infant sleeping on the stomach is more likely to overheat (hyperthermia) because his or her face and/or head are more likely to become covered. Researchers exposed mice to either condition or to a combination of the two conditions. Although neither hypoxia nor hyperthermia alone affected autoresuscitation, researchers noted an increased frequency of autoresuscitation failure at first exposure to hypoxia when the temperature was higher. In addition, they found decreased ability to recover from multiple exposures to hypoxia when the temperature was higher. These studies suggest that hypoxia and hyperthermia in combination may increase the risk posed by stomach sleep condition and by the head covered by bedding (*J Appl Physiol*, 2004; *97*, 669-674).

Previous research has shown that infants who are not accustomed to sleeping on the stomach are at significantly higher risk of SIDS when they are placed on the stomach for sleep. To understand more about this increased risk, researchers compared the protective behaviors of infants who were experienced sleeping on their stomachs with those of infants inexperienced with this sleep position. Infants with experience stomach sleeping had the best protective responses, turning the head or lifting the head, possibly to reach more oxygen-rich air or to reduce overall temperature. Not only did inexperienced infants move and lift their heads less often, they also spent more time with their faces in the bedding (*Pediatrics*, 2004; *114*, 1634-1639). These findings also indicate that some protective factors are learned, bolstering the theory that some infants who succumb to SIDS do not learn these behaviors. This absence of learning may result from deficits in the brain' components involved in learning, or from deficits in the ability to sense elevated carbon dioxide levels, preventing them from learning any type of protective behavior for the situation. The latter theory is consistent with the findings explained earlier related to abnormalities in the tissues of the brainstem, which mediates response to carbon dioxide levels.

Infants who sleep on their stomachs are reportedly slower to wake up in response to arousing stimuli compared to those who sleep on their backs and that stomach-sleeping infants spend more time in quiet or deep sleep. Such features could be related to deficits in the medullary system, which helps mediate arousal from sleep. In fiscal year 2005, researchers extended their findings related to stomach sleeping. They found that, even when stomach-sleeping infants are in active sleep (also called Rapid Eye Movement [REM] sleep), which is supposed to be easier to arouse from, their brain wave activity is slower in frequency, more closely resembling quiet sleep (*Arch Dis Child Fetal Neonatal Ed*, 2005; F311-F315). So infants who sleep on their stomachs are more often in a deeper sleep than infants who sleep on their backs, a finding which could explain why they take loner to arouse than their back-sleeping peers.

More than 90 percent of SIDS deaths occur in infants younger than six months of age, with peak incidence between two and four months of age. Researchers consider this timeframe to be a developmental period of unique vulnerability to environmental factors, such as sleeping on the stomach, that increase the risk of SIDS. To learn more about this timeframe, researchers examined life-sustaining functions controlled by the brainstem using the "tilt test"—rapidly tilting infants from the horizontal to the head-up position. When newborns were rapidly tilted to the head-up position, their reflexes increase the heart rate in response to the tilt. Recordings of brain waves done at the same time as the tilt showed an increase in electrical activity in the cerebral cortex, the area of the brain that integrates signals from all parts of the brain, including the brainstem. The heart rates of infants between two months and four months of age did not increase in response to the head-up tilt, and these infants showed a smaller increase in electrical activity in the brain compared to newborns (*Acta Pediatr*, 2005; *94*, 1756-1763). This developmental difference in response could result from a variety of reasons, which are now being investigated. Researchers suggest that the tilt test may be a good way to assess the brain's control of heart rate and blood pressure during the peak age of SIDS (*Acta Pediatr*, 2006; *95*, 77-81).

GENETICS AND SIDS

Although the risk for SIDS does not seem to have a large genetic component, some deaths diagnosed as SIDS may have defined genetic causes. Prior work supported by the NICHD found that 5 percent and 10 percent of SIDS cases had mutations in the *SCN5a*, a cardiac sodium-channel gene involved in long-QT syndrome. Recently, researchers detected other rare mutations in channel-associated proteins that result in cardiac-channel malfunction in some cases diagnosed as SIDS. Three new genes with different molecular pathologies are implicated in cases diagnosed with SIDS; the findings include *CAV3*, which encodes caveolin -3, a structural protein found in plasma membranes of muscle. The mutations observed in SIDS cases resulted in late sodium currents, a phenotype similar to that seen with mutations of *SCN5a*, that lead to prolonged QT. Of interest is that researchers isolated all three mutations from 50 SIDS cases among African American infants, but found none of the mutations in 83 cases of SIDS in white babies (*Heart Rhythm*, 2007; *4*, 161-166).

Mutations in the glycerol-3-phosphate dehydrogenase 1-like (*GDP1-L*) gene disrupt the trafficking of the *SCN5a* protein, resulting in a loss of sodium-channel function. Three mutations of *GDP1-L* were detected in 222 SIDS cases. When co-expressed with sodium-channel protein, the mutations significantly reduced sodium current; when transfected in cell culture, the mutations reduced sodium current density, which could lead to pro-arrhythmogenic conditions (*Circulation*, 2007; *116*, 2253-2259).

A different mutation in the *RyR2*-encoded cardiac ryanodine receptor causes lethal catecholaminergic ventricular tachycardia (CPVT), which is sometimes miscategorized as SIDS. When these mutations are present, cardiac calcium channels exhibit increased activity in response to sympathetic stimulation, making channels leaky and resulting in fatal cardiac arrhythmia. Such sympathetic stimulation can result from physiological stress, such as exertion, hypoxia, thermal stress, or even the sympathetic surge during REM sleep. Out of 143 unrelated SIDS deaths, two female SIDS infants had *RyR2* mutations and both died in their sleep. Both of

the mutated proteins, under simulated *in vitro* biochemical stress conditions, resulted in a gain of function in cardiac calcium channel consistent with prior-characterized CPVT-associated *RyR2* mutations *Heart Rhythm*, 2007; *4*, 733-739). This type of "molecular autopsy" is proving to be an important strategy in unraveling the pathophysiology of deaths diagnosed as SIDS.

COLLABORATIVE HOME INFANT MONITORING EVALUATION (CHIME) STUDY

The CHIME Study, now complete, was a multi-center cooperative study of home monitoring to determine whether the monitoring could detect SIDS and other life-threatening events in high-risk infants. Almost 1,200 infants were enrolled in the following subject groups: healthy term infants; preterm infants weighing less than 1,750 grams at birth; and siblings of babies who had died from SIDS or who experienced an idiopathic apparent life-threatening event. The PPB, CHIME researchers, and industry collaborated in the development of new monitoring technology, which was being tested for its potential to detect and record life-threatening cardiorespiratory episodes.

The technology incorporated new, advanced computer capabilities, inductance plesthysmography, electrocardiogram (ECG), pulse oximetry, and an accelerometer to detect motion and infant position. In addition to event recording, which captured physiology for a period before, during, and after an event, monitors were programmed to store continuous RR intervals from the ECG, continuous breath-breath intervals, and normative three-minute epochs at hourly intervals. Findings from CHIME published in 2001 indicated that cardiorespiratory events (e.g., apnea, bradycardia, etc.) meeting conventional alarm thresholds were quite common, even in healthy term infants. More severe events were common only in preterm infants, and the timing of the events suggested that they were likely not immediate precursors of SIDS (*JAMA*, 2001; *285*, 2199-2207). However, further research showed an association between infants who had five or more events exceeding conventional or extreme alarm thresholds and lower scores on the Bayley Scale at one year of age compared to infants who had fewer or no events (*J Pediatr*, 2004; *145*, 465-471).

To prevent occurrences of these events and poor long-term outcomes, it is necessary to understand their origins. Recently, CHIME investigators reported on in-depth analyses of cardiorespiratory and oxygen saturation changes in the two hours prior to an event. The duration of respiratory pauses and of periodic breathing progressively increased just before conventional events; respiratory rate variability increased immediately before a conventional event and at one hour before an extreme event; and oxygen saturation decreased immediately before both conventional and extreme events. Thus, apnea and bradycardia are preceded by autonomic instability of the cardiorespiratory system (*Pediatr Pulmonol*, 2008; *43*, 87-98).

Risk Reduction

Established by the NICHD in 1994, the *Back to Sleep* campaign is a partnership with the AAP, First Candle/SIDS Alliance, the Association of SIDS and Infant Mortality Programs, the Maternal and Child Health Bureau at the Health Resources and Services Administration, and other organizations for the support of a public health education campaign to educate parents and caregivers about ways to reduce the risk of SIDS based on the recommendations from the AAP Task Force on SIDS. When it was initiated, the campaign's primary message

was that healthy babies be placed on their back or sides to reduce the risk of SIDS; today, *Back to Sleep*'s main message is that all babies be placed wholly on their backs for every sleep to reduce the risk of SIDS.

In 2005, the AAP Task Force on SIDS added a recommendation against bed sharing as a result of evidence related to the hazards of this practice in relation to SIDS and infant mortality (*Pediatrics*, 2005; *116*, 1245-1255). Findings from the Infant Care Practices Study, a longitudinal prospective study of more than 15,000 mother-infant dyads enrolled at birth in Massachusetts and Ohio from 1995 to 1998, provided information about bed-sharing practices in the United States. The study indicated that the proportion of women who reported bed sharing for most of the previous night decreased from 22 percent when the infant was one month old to 13 percent and 14 percent when the infant was three months old and six months old, respectively. Breastfeeding was a strong predictor of bed sharing at all infant ages; this association was strongest for Asian and while women. The likelihood of bed sharing was high among African American dyads independent of breastfeeding. This finding was concerning for researchers because the risk of SIDS associated with bed sharing seems to be greatest for the youngest infants (*J Dev Behav Pediatr*, 2004; *25*, 141-149).

The AAP Task Force also added a recommendation about using a clean, dry pacifier in its 2005 recommendations. In addition to a large body of evidence from international studies that pacifiers reduce the risk of SIDS, a population-based case-controlled study conducted in 11 counties in California provided further support for this recommendation. The study which evaluated SIDS risk since the start of the *Back to Sleep* campaign, reported a 0.08 adjusted odds ratio (95% CI: 0.03-0.21) for SIDS associated with pacifier use during last sleep. These statistics mean that the risk of SIDS among infants who used pacifiers was one-twelfth that of infants who did not use pacifiers. Pacifier use was associated with risk reduction in every sociodemographic category and risk factor evaluated (*BMJ*, 2006; *332*, 18-22).

In order to evaluate changes in infant care practices in response to the AAP recommendation and to the *Back to Sleep* campaign, the NICHD has supported the National Infant Sleep Position (NISP) Study. This annual telephone survey of nighttime caregivers in households with infants younger than eight months of age has documented a decline in the number of infants placed to sleep on their stomachs; this decline correlates with the decline in SIDS rates (see Figure 7). In the era of the campaign, the SIDS rate has dropped by more than 50 percent, and, according to NISP data, about three-fourths of caregivers indicate placing infants to sleep on their backs. According to the National Center for Health Statistics, the SIDS rate for 2004 was about 0.5 deaths per 1,000 live births, a decline of more than 50 percent since the *Back to Sleep* campaign began.

NISP National Infant Sleep Position

However, although SIDS rates have dropped at similar rates in all race/ethnicities, a disparity in SIDS rates remains—namely, the rate of SIDS among African Americans is more than twice that of whites. The NICHD is conducting research to understand why this and other disparities in SIDS rates exist. For example, researchers conducted interviews at Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) clinics in Boston, Dallas, Los Angeles, and New Haven. WIC is a federally funded program for low-income women who are

pregnant, breastfeeding, and/or postpartum and for children who are younger than five years of age and are from low-income families. Findings from this study (*Pediatrics*, 2006; *118*, e243-250) include the following:

- Approximately two-thirds of women attending the clinics in this study were African American.
- 59 percent of all women reported that they placed the baby on his or her back to sleep.
- There were differences among locations, with 78 percent of all women usually placing infants on their backs to sleep in New Haven, 61 percent in Boston, 52 percent in Los Angeles, and 45 percent in Dallas.
- Only 36 percent overall reported that a doctor recommended that they place the baby on its back to sleep.
- Women were more likely to place the baby to sleep on its back if they trusted the doctor or if they received a recommendation from the doctor or nurse.
- About half of women were concerned that the baby would choke while sleeping on its back, and these women were less likely to place the infant on the back to sleep.
- Advice from a relative or female friend and perceived comfort for the baby were most influential in determining the sleep position for the baby.

This study revealed that it is possible to achieve high rates of back sleeping among African Americans. The study also reinforced what the NICHD and other agencies are currently doing—that is, conducting community education programs that focus on disseminating safe sleep messages so that friends and family members embrace them and share them. Other NICHD programs focus on educating doctors and nurses to provide advice in an atmosphere of trust. A key aspect of these programs is information to help dispel myths about choking.

BRANCH ACTIVITIES: COOPERATIVE AGREEMENTS

The PPB has a number of cooperative agreements to facilitate and encourage large-scale research requiring multi-center networks.

In 1986, in response to the need for well-designed clinical trials in maternal-fetal medicine and neonatology, the NICHD established two large-scale Networks—the NRN and the MFMU Network—as administrative frameworks in which to conduct multi-center, randomized clinical trials and other prospective clinical studies in obstetrics and neonatology. Each Network is guided by a Steering Committee, which consists of representatives from each clinical site, from the PPB, and from the data coordinating center. These Networks allow for timely and cost-effective responses to urgent clinical questions. Currently, the NRN has 16 sites, and the MFMU Network has 14 sites. Sites are selected every five years following an open competition.

Typically, each Network has two or three randomized controlled trials and two or three observational studies ongoing at any given time. Network investigators agree to use common

protocols, definitions, and data forms and are linked by their common data centers and common data-entry systems. Investigators, together with the PPB and the data coordinating center staff, develop protocols that are reviewed by advisory boards, external reviewers, and Data Safety and Monitoring Committees, which are established for each Network to ensure that the trials are safe and scientifically significant.

Advantages to doing clinical trials within the Networks include the following.

- The Networks provide large populations with which to conduct studies that have adequate statistical power to resolve many research questions; inadequate sample size is a common limitation of many published clinical trials. Approximately 140,000 births occur per year in the MFMU Network, and 105,000 infants are born each year in the NRN.
- Because the study populations are diverse, a therapy or management strategy shown to be effective across an array of ethnic and socioeconomic backgrounds and health care settings within the Networks is more likely to prove effective in real-world clinical practice.
- The data coordinating centers attached to the Networks have sufficient resources to assure excellent study management and data quality.
- The administrative systems of the Network are efficient and cost effective. To ensure their cost effectiveness, the Networks are funded through a combination of a minimum base budget and capitated funds for enrollment in specific protocols. New trials can begin relatively rapidly because the infrastructure is already in place.

The Networks address the need for clinical trials in neonatology and obstetrics, especially trials related to preventing low birth weight (< 1,500 grams) and to the management of low birth weight infants. The Networks build upon contributions to the clinical trial field and are unique in that they rely, to a greater extent, on shared responsibility and commitment.

In addition to the long-term Networks, the PPB has implemented five additional time-limited Networks since 2005. These projects were designed to address specific questions and are time limited, meaning once the questions specific to their missions are addressed, the Networks will not recompete. The successes of these Networks are measured by their study and trial designs, the impact and number of their publications, and the incorporation of their findings into clinical practice and as the basis for additional studies. The following section describes PPB-supported Networks and other efforts funded through cooperative agreements.

NEONATAL RESEARCH NETWORK (NRN)

As explained earlier, the primary objective of the NRN is to advance the field of neonatal-perinatal medicine by establishing and maintaining a network of academic centers that perform multi-center clinical protocols in a rigorous manner to investigate the safety and efficacy of treatment and management strategies to care for newborn infants, including low birth weight infants. This model of multi-site clinical centers for research is the gold standard for conducting clinical research; the infrastructure is set up for the ideal randomized double-blinded placebo-controlled

trials and provides the ability to follow short-term (clinical effect) and long-term (neurodevelopmental outcome) measures. The Network is also set up for observational, longitudinal studies in the NICU setting. This scientific partnership has become an influential and successful enterprise in neonatal research. NRN members and co-investigators present regularly at national and international scientific meetings (see Figure 8 and Figure 9).

Randomized Controlled Trials

Since 2004, the PPB-supported NRN has conducted a number of clinical trials (see Figure 9); several of these trials and their outcomes are described below:

- The Network completed a high-impact trial of whole-body hypothermia for reducing death or disability in term infants who had acute perinatal asphyxia at 18 months of age (n = 208). Whole-body cooling reduced death and disability from 62 percent to 44 percent at 18 months of age (*NEJM*, 2005; *353*: 1574). This landmark study led the AAP to issue practice recommendations (*Pediatrics*, 2006; Mar;*117*[3]: 942-948) following publication of the beneficial finding.
  - Among neonates diagnosed as having hypoxic-ischemic encephalopathy (HIE), the classification and regression tree model, but not the scoring system, was superior to early neurologic examination in predicting death/disability. The three models were comparable in predicting death. Only a few components of the early neurologic examination were associated with poor outcomes. These scoring systems and classification trees, if validated, may help assess prognosis and may prove useful for risk-stratification of infants with HIE for clinical trials (*Pediatrics*, 2006; Nov;*118*[5]: 2084-2093).
  - School age followup (ages six to seven years) is underway for the valuable cohort of children included in the whole-body cooling trial. Long-term followup is currently scheduled to be completed in spring 2010. Several secondary analyses are also being performed.
  - Following completion of the previous study, the researchers will conduct an amplitude-integrated electroencephalogram study utilizing a cohort from the whole-body cooling trial and infants with HIE at NRN sites as followup of children at 18 months of age.
  - A new hypothermia trial testing the efficacy and safety of whole-body cooling in infants with HIE who present at 6 hours to 24 hours of age (just beyond the window of the previous study) began in 2008.
- The Network published its findings from a trial utilizing inhaled NO in sick, preterm infants. The results showed no benefit of inhaled NO in infants at < 1,500 grams birth weight also had respiratory failure (*NEJM*, 2005; Jul7;*353*[1]: 13-22).
  - Following cessation of the trial due to an interim analysis, cranial ultrasounds underwent a rigorous process of evaluation by a central reader. The results showed increased intraventricular hemorrhage (IVH) in infants exposed to inhaled NO, but the increase did not remain statistically significant after all subjects were evaluated. The findings demonstrate reliability and accuracy of highly unfavorable cranial ultrasound findings, but suggest caution when interpreting mild to moderate IVH or white-matter injury (*J Pediatr*, 2007; Jun;*150*[6]: 592-596, 596.e1-e5).

  - Followup showed that, among this extremely ill cohort, inhaled NO did not reduce death or neurodevelopmental impairment, nor did it improve neurodevelopmental outcomes (*J Pediatr*, 2007; Jul;*151*[1]: 16-22, 22.e1-e3).

- The Network previously completed a trial to evaluate the effect of parenteral glutamine supplementation on the risk of death or late-onset sepsis in extremely low birth weight (ELBW) infants (n = 1,433). Results indicated that such supplementation had no effect on death or sepsis (*Pediatrics*, 2004; 113).
  - Secondary studies are utilizing this important dataset to evaluate nutritional information for ELBW infants. Early provision of amino acids is associated with better growth at 36 weeks' post-conceptual age (*J Pediatr*, 2006; Mar;*148*[3]: 300-305). Higher fluid intake and less weight loss during the first 10 days of life were associated with an increased risk of bronchopulmonary dysplasia (BPD) (*J Pediatr*, 2005; Dec;*147*[6]: 786-790). Beneficial effects of breast milk on neurodevelopment were evident at 18 months' (*Pediatrics*, 2006; Jul;*118*[1]: e115-e123) and 30 months' (*Pediatrics*, 2007; Oct;*120*[4]: e953-e959) corrected age in ELBW infants. Nutrition management remains a significant problem for this population.
  - A cytokines study was conducted concurrently with this previous trial. Measurements of cytokine values in ELBW infants may give insight into short- and long-term complications of preterm birth.

- The NRN completed a CPAP delivery room pilot study of ELBW infants (n = 103) (*Pediatrics*, 2004; Sep;*114*[3]: 651-657) that showed the feasibility of applying CPAP following stabilization after delivery. This pilot study led to a large multi-center trial called the Surfactant Positive Airway Pressure and Pulse Oximetry (SUPPORT) Trial in ELBW infants. This large-scale, factorial design CPAP/surfactant and oxygen-saturation level trial has recruited approximately two-thirds of the needed 1,300 infants and is co-funded by NHLBI.
  - Secondary studies attached to this trial include a neuroimaging study, an antenatal consent study, a growth study, and a breathing outcomes study, as well as followup at 18 months' to 22 months' corrected age.

- The Network completed a benchmarking protocol to reduce BPD in VLBW infants (< 1,250 grams) (*Pediatrics*, 2007; May;*119*[5]: 876-890). Benchmarking and multimodal quality improvement changed practices, but did not reduce BPD rates. Multiple secondary studies have been performed including those listed below:
  - NRN researchers developed a significant finding, utilizing a physiologic definition of BPD that relied on oxygen saturation criteria reduced the overall rate of BPD and reduced the variation among centers. Researchers found significant center differences in terms of the impact of the physiologic definition; differences between centers remained even with the use of this standardized definition. The magnitude of the change in BPD rate was comparable to the magnitude of treatment effects seen in some clinical trials of BPD. The physiologic definition of BPD facilitates the measurement of BPD as an outcome in clinical trials and the comparison between and within centers over time (*Pediatrics*, 2004; Nov;*114*[5]: 1305-1311).

  - Researchers found that cumulative exposure to hypocarbia, but not hyperoxia was independently related to risk of periventricular leukomalacia in low birth weight infants (*Pediatrics*, 2006; Oct;*118*[4]: 1654-1659).
  - Prescription of oxygen with combinations of flow rates and concentrations that delivered a low-dose of effective Fraction of Inspired Oxygen (FiO2) is common in patients who receive nasal canula oxygen in the nursery. Routine calculation of effective FiO2 values may prompt earlier trials of room air and, thus, reduce unnecessary days of oxygen therapy (*Pediatrics*, 2005; Oct;*116*[4]: 857-861).

- Retinopathy of prematurity (ROP) is a devastating disease that causes severe visual impairment and/or blindness in very preterm infants. The NRN is conducting a series of studies, including documentation of inositol blood levels and single- and multiple-dose pharmacokinetic studies, that will lead to a large clinical trial to determine if inositol is useful as a preventive agent for ROP. This study is co-funded by the NEI.
- The Early Onset Sepsis (EOS) Surveillance Study is being performed in collaboration with the CDC. The objectives of this study are to: establish current hospital-based rates of EOS among term and preterm infants in the era of intrapartum antibiotic prophylaxis; monitor the organisms associated with EOS and meningitis in neonates of all birth weights and GAs; compare asymptomatic and symptomatic infants by GA and pathogen; and monitor sepsis-associated mortality rates for infants with EOS by pathogen group.
- Inhaled Prostaglans E_1 pilot study is a randomized, placebo-controlled, clinical trial to test the safety of using intravenous prostaglandin E1 (PGE1) in an inhaled form for treatment of hypoxemic respiratory failure in term newborns. The study will enroll 50 infants diagnosed with hypoxemic respiratory failure at nine NRN sites and will randomly assign them to receive one dose over a 72-hour period of either high-concentration PGE1, low-concentration PGE1, or placebo. In addition to determining the safety, optimal dose, and duration of the therapy, this pilot trial will evaluate the feasibility of conducting a larger, multi-center randomized, blinded placebo-controlled trial of the same treatment.
- A randomized trial of phototherapy for jaundice in ELBW infants was recently completed and analyses and manuscripts are in process.

Observational Studies

In addition to clinical trials, the NRN has completed a number of observational studies, including those listed below:

- One NRN observational trial of necrotizing enterocolitis (NEC) showed that survival to hospital discharge after surgery for NEC or intestinal perforation was poor at 51 percent. Followup at 18 months showed continued poor outcome and a high rate of impairment in survivors. Surviving children who underwent laparotomy were less likely to have neurodevelopmental impairment (38 percent) than those who underwent intestinal drain placement (63 percent). Differences between the drain and laparotomy groups included GA and birth weight, providing evidence for a randomized trial of peritoneal drain versus laparotomy with 18-month neurodevelopmental outcome as a primary endpoint. This second trial is under development in the NRN.
- The Network recently completed enrollment in an observational trial of *Candida* infection; data entry and analyses are forthcoming.

- An observational trial of a pneumococcal vaccine conjugate in VLBW infants recently completed enrollment. Followup is completed and analyses are forthcoming.
- The NRN has a database of preterm infants who were admitted to Network sites and a follow-up program for infants born at ELBW. One of the most important Network efforts using these resources is the development and implementation of a standardized follow-up protocol for evaluating outcomes of ELBW infants at 18 months' to 22 months' corrected age. The follow-up protocol provides the largest standardized follow-up assessment of ELBW infants to date. Seminal publications from the last four years include the following:
  - Sepsis in VLBW infants resulted in higher rates of neurodevelopmental impairment than was seen in an uninfected cohort of infants. Results from this large cohort study (n = 6,093) suggest that neonatal infections among ELBW infants are associated with poor neurodevelopmental and growth outcomes in early childhood. Additional studies are needed to elucidate the pathogenesis of brain injury in infants with infection so that novel interventions to improve these outcomes can be explored (*JAMA*, 2004; Nov17;*292*[19]: 2357-2365).
  - Evidenced-based outcome information for infants born at 22 weeks' to 25 weeks' gestation showed that multiple factors in addition to GA can determine resultant outcome for ELBW infants. Use of multiple factors, including sex, estimated birth weight, single versus multiple gestation, and antenatal corticosteroid administration in addition to GA gives better survival and impairment-free survival estimates for infants at 22 weeks' to 25 weeks' gestation (*NEJM*, 2008; *358*[16]: 1672-1681). This study resulted in a Web-based tool for outcome data that is available on the NICHD Web site, at http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/index.cfm, for medical staff and lay persons to use to make informed decisions regarding care among ELBW infants.
- Additional highlights of published information from observational studies include:
  - Researchers saw no significant increases in survival without neonatal and long-term morbidity among VLBW infants between 1997 and 2002. They speculate that improving survival without morbidity requires not only determining, disseminating, and applying best practices using therapies currently available, but also identifying new strategies and interventions (*Am J Obstet Gynecol*, 2007; Feb; *196*[2]: 147.e1-e8).
  - Histamine type 2-blocker therapy was associated with higher rates of NEC, a result which agreed with a previous randomized trial of acidification of infant feeding resulting in a decreased incidence of NEC. In combination, these data support the hypothesis that gastric pH level may be a factor in the pathogenesis of NEC (*Pediatrics*, 2006; Feb;*117*[2]: e137-e142).
  - Researchers found significant neurodevelopmental impairment in preterm birth survivors despite significant strides in the care and management of these vulnerable infants: Perinatal, neonatal, and early childhood factors confer similar incremental risk or protection to boys and girls, but boys appear to have inherently greater baseline risk. Unmeasured biological variables likely contribute to the neurodevelopmental outcome disadvantage of preterm males. (*Acta Paediatr*, 2006; Oct;*95*[10]: 1239-1248).
  - One study showed that childhood neurodevelopmental outcomes among infants younger than 25 weeks of estimated GA are not improving in the post-surfactant era, despite more aggressive perinatal and neonatal treatment (*Pediatrics*, 2005; Jun;*115*[6]: 1645-1651).

- Among ELBW infants, receiving surgical management of NEC (SurgNEC) was associated with significant growth delay and adverse neurodevelopmental outcomes at 18 months' to 22 months' corrected age compared with receiving no treatment for NEC (NoNEC). Medical management of NEC (MedNEC) conferred additional risk. SurgNEC was also likely to be associated with greater severity of disease (*Pediatrics,* 2005; Mar;*115*[3]: 696-703).
- At 18 months' to 22 months' corrected age, ELBW infants born with major anomalies had nearly twice the risk for neurodevelopmental impairment, as well as increased risk of poor growth and more than three times greater risk of rehospitalization when compared to ELBW infants without major anomalies. This information may be valuable for counseling parents regarding the outcomes of these infants and for the facilitation of appropriate support and intervention services (*Pediatrics,* 2007; Dec;*120*[6]: e1512-e1519).
- Preterm infants were at increased risk for rehospitalization after discharge. Although racial disparities are known to exist in pediatric health care, in a cohort of ELBW infants recruited from 1998 to 2000, race was not a predominant variable in the risk for rehospitalization. Medical morbidities and low family income seemed to be the major risk factors for rehospitalization.

Data from the following completed NICHD NRN studies are available upon request:

- Intravenous gamma globulin trial in ELBW infants
- Randomized trial of parenteral glutamine supplementation for ELBW infants
- Inhaled NO for preterm infants with severe respiratory failure
- Randomized controlled trial of induced hypothermia for HIE in term infants

The NRN has also conducted several trials with the following industry partners:

- INO Therapeutics, Inc., provided inhaled NO for the NO studies.
- Natus Medical, Inc., provided NeoBlue light emitting diode phototherapy lights for use in the phototherapy trial.
- Abbott Laboratories' Ross Products Division provided the study drug for the ROP cross-sectional and single-dose studies. It will also provide inositol for the upcoming multi-dose studies.

The NRN Data Coordinating Center underwent competitive review and was awarded in 2008. The NRN will undergo competitive review in 2011; additional information on the Network is available at http://neonatal.rti.org.

MATERNAL LIFESTYLES STUDY (MLS)

MLS is the largest clinical, prospective, longitudinal study of prenatal drug exposure and child outcomes to date. It is conducted at four NRN sites: University of Miami, University of Tennessee at Memphis, Wayne State University, and Brown University. The cohort includes

658 exposed and 730 comparison mother/child dyads. In addition to PPB support, NIDA has consistently co-funded the MLS effort since it began.

In Phase I of the MLS, 19,079 pregnant mothers were recruited just before or immediately after they gave birth. Of these, 16,988 (89 percent) met basic eligibility criteria, and 11,811 (70 percent) agreed to participate in the study. Drug use was confirmed by an interview with the mother and by gas chromatography/mass spectroscopy for cocaine/opiate metabolites in the meconium of the infant. Based on this information, 1,185 infants (10 percent) were exposed to either cocaine or opiates during pregnancy. A total of 7,442 infants (63 percent) were confirmed as not having been exposed to either cocaine or opiates; the exposure status of 3,184 infants (27 percent) was not confirmed. The use of alcohol, tobacco, and/or marijuana by the mother occurred in all three of these groups.

Phase II of the study tracked the development of infants who had been exposed to illicit drugs and compared the results to those for infants who were not exposed to illicit drugs. A total of 1,388 subjects were recruited for this phase of the MLS. Of these, 658 infants were exposed to cocaine, opiates, or both *in utero*, while 730 infants had been exposed to neither. All of these infants were initially assessed at one month of age; mothers or caretakers were encouraged to participate in visits when the child was four months, eight months, 10 months, 12 months, 18 months, 24 months, 30 months, and 36 months of age. During these visits, the children participated in a variety of assessments to determine their medical and developmental outcomes over time. Researchers also asked mothers and caretakers questions about the infants and the environment in which the children lived.

Mother/child dyads have continued their involvement in the MLS through subsequent phases. Phase III assessed children at ages four years through seven years. Phase IV includes children between the ages of eight years and 11 years. Phase V (ages 12 years to 15 years) was recently funded by NIDA. The NICHD continues to support the Data Coordinating Center and the Neurobattery Center for this longitudinal study.

MATERNAL-FETAL MEDICINE UNITS (MFMU) NETWORK

Like the NRN, the MFMU Network's scientific partnership between the PPB, the funded maternal-fetal medicine divisions, and the data coordinating center has also become a strong force in the obstetric research community. Network members present regularly at national and international scientific meetings and have published more than 140 papers in peer-reviewed journals. The MFMU Network marked its 20th anniversary in 2006. The efforts of the committed individuals affiliated with the Network during the past two decades have yielded success in changing obstetrical practice by identifying new therapies and evaluating technologies used in maternal-fetal medicine, while also helping to abolish practices that are not useful (see Figure 10, Figure 11, and Table 2).

Evaluations of Common Medical Practices

Challenges remain related to investigating problems in clinical obstetrics, particularly those related to prevention of low birth weight, prematurity, and medical problems of pregnancy. The MFMU Network continues to rise to the challenge of designing programs and treatments for the prevention of preterm birth and for the improvement of maternal and infant outcomes using evidence-based medical practices.

In October 2007, the ACOG Committee Opinion for subclinical hypothyroidism in pregnancy did not recommend routine screening for the condition. However, based on the potential for neurodevelopmental problems in the children whose mothers have thyroid deficiency during pregnancy, some national societies and public interest groups still recommend screening and treating women during pregnancy for subclinical hypothyroidism despite the lack of evidence to support this practice. To address these concerns, the MFMU Network designed a randomized, double-blind clinical trial to determine whether thyroxine treatment for women with subclinical hypothyroidism or hypothyroxinemia diagnosed during the first half of pregnancy is associated with intellectual improvements in their offspring at age five years, as measured by the Wechsler Preschool and Primary Scale of Intelligence. The researchers recruit women with singleton pregnancies between 8 weeks' and 20 weeks' gestation and conduct blood tests to determine whether subclinical hypothyroidism or hypothyroxinemia is present. Enrolled patients take levothyroxine supplements (thyroid replacement) or placebo daily until delivery. Blood draws are conducted during regularly scheduled study visits, and dosages are adjusted based on test results. The children born to enrolled patients will undergo developmental testing each year until age five years. Recruitment began in October 2006 and, to date, more than 40,000 women have been screened and 640 were enrolled. It is anticipated that data collection will continue until 2014.

PRETERM DELIVERY AND 17 A-HYDROXYPROGESTERONE CAPROATE (17-OHPC)

As explained in the Branch's previous report to the NACHHD Council, MFMU Network researchers made a groundbreaking finding related to preterm delivery and 17-OHPC—namely that weekly injections of the treatment reduced preterm birth rates by 34 percent among women who had a previous preterm singleton delivery compared to placebo. Further research confirmed that 17-OHPC successfully reduced the risk of recurrent preterm delivery in a subset of high-risk women and improved neonatal outcomes for infants born to these women. Since the initial finding was published, the MFMU Network has conducted these related studies:

- The efficacious formulation of 17-OHPC is unknown, and 17-OHPC is currently not commercially available. The MFMU Network efforts resulted in a private company submitting a New Drug Application to the FDA to produce 17-OHPC. In response, the FDA requested that the MFMU Network followup on the children from the trial to ascertain the health and developmental outcomes for those exposed to 17-OHPC *in utero* versus those exposed to placebo. Of the offspring from the original trial, 80 percent (278) were available for followup, which consisted of a physical examination and developmental testing. The mean age at followup was four years. This followup indicated no significant differences in developmental and physical outcomes (including genital abnormalities) between the two groups. The private company continues to work with the FDA to bring this product to market.

- The Network also studied omega-3 fatty-acid supplementation to prevent preterm birth in high-risk pregnancies. The aim of this double-masked randomized clinical trial was to determine whether omega-3 fatty acids, in conjunction with 17-OHPC injections, reduced the risk of preterm birth in women at high risk for spontaneous preterm delivery.
  - Eligible women with singleton pregnancies at 16 weeks' to 21 6/7 weeks' GA and who had a previous singleton spontaneous preterm delivery were randomized to either 250 mg 17-OHPC weekly and 2,000 mg omega-3 daily or placebo plus 250 mg 17-OHPC weekly and 2,000 mg mineral oil daily.
  - Primary outcome was preterm delivery less than 37 weeks of gestation; secondary was a composite neonatal outcome.
  - Although designed as a three-year study, the trial ended more than one-and-a-half years earlier than expected.
  - Results, presented at the 2008 SMFM meeting, indicated that, among women with a prior spontaneous preterm birth, 17-OHPC/omega-3 supplementation did not reduce the rate of preterm birth. However, an association between dietary intake of fish and reduced preterm birth was observed. The manuscript has been submitted to a peer-reviewed journal.
- The rate of multi-fetal pregnancies, with higher risk of preterm birth and associated morbidity and mortality, is increasing in the United States and is most likely the result of increases in assistive reproductive technologies. To date, no intervention exists to prevent preterm birth in this population. The Network conducted a randomized controlled trial to evaluate whether 17-OHPC reduced the rate of preterm birth in twin and triplet gestations.
  - More than 600 women were assigned to either 17-OHPC or placebo.
  - Results showed no significant differences between the groups within the twin cohort in terms of delivery or fetal death before 35 weeks' gestation and serious adverse fetal or neonatal events.
  - Although the results of this part of trial were negative, the findings are important for the obstetric community because they indicate further studies are warranted to determine whether 17-OHPC is effective for reducing preterm birth for other pregnancies in which preterm birth is likely. This manuscript was published in *The New England Journal of Medicine* in 2007 (Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, & Spong CY, et al for the NICHD MFMU Network. [2007]. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *NEJM*, 357, 454-461).
- A previous Network study, conducted in the late 1990s, concluded that shortened cervical length at 16 weeks' to 18 weeks' gestation predicted spontaneous preterm delivery at less than 35 weeks' gestation in women with a prior early spontaneous delivery (*JAMA*, 2001; *286*: 1340-1348). Utilizing the results of this study, the Network designed a trial to determine whether 17-OHPC, initiated after 16 weeks but before 23 weeks of gestation, reduced the risk of a preterm delivery (before 37 weeks' gestation) in nulliparous women with short cervices (less than 30 mm).
  - Using transvaginal ultrasound, the researchers are screening women who are pregnant for the first time (or who have not had a pregnancy lasting more than 19 weeks' gestation) to see if their cervices are short (less than 30 mm).

- Those with shortened cervices will be randomized to weekly 17-OHPC or placebo.
- The study began in March 2007 and has a sample size of 800. More than 5,000women have been screened and 150 enrolled to date.

CESAREAN DELIVERIES AND VAGINAL BIRTH AFTER CESAREAN (VBAC)

The rate of cesarean delivery has risen dramatically during the past two decades and currently ranks as the most commonly performed surgical procedure in the United States. A substantial portion of women who undergo a cesarean delivery have a history of a previous cesarean delivery, but some women who have had a previous cesarean deliver their infants by VBAC. Existing evidence about the risks and benefits of VBAC that could assist health care providers in counseling women with a history of a prior cesarean delivery is not current and is generally derived from small studies. The MFMU Network chose to use its large patient population, specifically in the MFMU Cesarean Registry, to study the outcomes of VBAC, including complications, fetal injury, and contributing factors.

- The MFMU Cesarean Registry, completed in December 2002, includes observational data on more than 52,000 primary and repeat cesarean deliveries and more than 18,000 VBAC deliveries.
- This Registry provides the largest resource of information on cesarean deliveries collected in a standardized, prospective fashion by trained study personnel.
- The study found that women who attempted trial labor had significantly higher rates of maternal morbidity (i.e., uterine rupture, endometritis, and transfusion) and neonatal complications (i.e., HIE) compared with women who underwent an elective repeat cesarean delivery. Because serious maternal morbidity increases progressively with number of cesarean deliveries, the number of anticipated pregnancies should be considered when counseling women regarding elective repeat cesarean versus a trial of labor. These findings may be important when counseling patients regarding elective cesarean versus trial of labor after previous cesarean delivery.
- These findings, in part, led to the 2006 release of the ACOG Committee on Obstetric Practice Committee Opinion *Induction of Labor for Vaginal Birth After Cesarean Delivery*, which states:
  - Induction of labor in women who have had cesarean deliveries may be necessary because of fetal or maternal indications. The potentially increased risk of uterine rupture should be discussed with the patient and documented in the patient record. Selecting women most likely to give birth vaginally and avoiding the sequential use of prostaglandins and oxytocin appear to offer the lowest risks (Number 342, August 2006).
- In a study to evaluate the success rate and risks for women with twin pregnancies who attempted a trial of labor following at least one previous cesarean delivery, the Network ascertained data on 412 women pregnant with twins who had a prior cesarean delivery.
  - Of these, 226 had elective repeat cesarean delivery. Of the 186 women who attempted to deliver vaginally, 64.5 percent were successful. Almost half of the women who had a failed trial of labor had vaginal delivery for twin A and cesarean for twin B. There were no differences in maternal morbidity (i.e., transfusion, endometritis, NICU admission, uterine rupture) for those who attempted vaginal delivery versus those who elected for repeat cesarean delivery.

- This study showed that, for women pregnant with twins who have a history of a prior cesarean, a trial of labor is a reasonable consideration for selected pregnancies at or near term and does not increase maternal morbidity.

Because cesarean delivery is one of the most common operations performed in the United States, the Network evaluated anesthesia-related complications in cesarean deliveries. Regional anesthesia has become the anesthetic method of choice in obstetrics. Researchers assessed anesthetic use and complications in more than 37,000 women who underwent cesarean delivery and found that regional anesthetic was used in 93 percent of these deliveries; morbidity related to the procedure was rare. Increased maternal weight, higher preoperative risk, rapid decision-to-incision interval, and placement later in labor were related to increased risk of failed regional procedure. Only one maternal death was directly implicated to anesthesia, due to a failed intubation. The results indicate that obstetric anesthesia for cesarean delivery is safe and rarely results in procedure-related complications.

The Network also evaluated the decision-to-incision intervals and related them to maternal and neonatal outcomes using a cohort of women who underwent emergency cesarean deliveries. For most practitioners, the goal for emergency deliveries is for a cesarean to begin within 30 minutes of the decision to operate, even though the ACOG/AAP guideline on emergency cesarean delivery does not support the position that all cesareans must be performed within 30 minutes of the decision. Of the 11,481 primary cesarean deliveries, 2,808 were performed for an emergency indication; of those with emergency indication, 65 percent of deliveries began less than or equal to 30 minutes from the decision to operate and 35 percent began at more than 30 minutes from the decision to operate. Most of the deliveries occurring at more than 30 minutes after the decision to perform a cesarean were performed because of nonreassuring fetal heart rate tracings. Adverse neonatal outcomes were not increased in this group. Even though this large, multi-center study found that approximately one-third of emergency primary cesarean deliveries began more than 30 minutes after the decision to operate, more than 95 percent of these infants did not experience newborn compromise. Overall, in the setting of emergency delivery, the decision-to-incision interval did not appear to impact maternal or neonatal complications, supporting the ACOG/AAP guidelines for emergency cesareans.

OTHER MFMU NETWORK EFFORTS

As a result of an ACOG Practice Bulletin issued in 2001, universal screening and treatment of gestational diabetes mellitus (GDM) are widely practiced by the obstetrical community. To evaluate the true benefit of such screening and treatment, the MFMU Network conducted a randomized clinical trial to determine whether daily self blood-glucose monitoring and diet therapy reduced neonatal morbidity, including reducing the risk of problems for newborns, such as low blood sugar, jaundice, macrosomia, and other pregnancy outcomes, in women with mild GDM. The primary outcome composite included hypoglycemia, hyperinsulinemia, hyperbilirubinemia, birth trauma, death, or stillbirth. Eligible women between 24 weeks' and 31 weeks' gestation diagnosed as having mild GDM were enrolled to either receive standard pregnancy care or diet therapy with self-administered blood sugar monitoring. Enrollment ended in November 2007, with 1,889 study subjects. Analyses of the data are ongoing. The knowledge gained from this study may help improve treatment and outcomes for women diagnosed with mild GDM.

The MFMU Network also builds upon information obtained from its own studies. In 2000, the NIH panel for the consensus development conference *Antenatal Corticosteroid Revisited: Repeat Courses* concluded that the available data was inadequate to recommend the repeated use of antenatal corticosteroid therapy for women at risk of preterm birth (see http://consensus.nih.gov/cons/112/112_intro.htm). Follow-up studies indicated that repeated exposure to antenatal corticosteroids significantly reduced specific neonatal morbidities, but did not improve composite neonatal outcome, decreased birth weight, and increased the risk of SGA neonates. Therefore, routine weekly repetition of antenatal steroids for women at high risk for preterm birth could not be justified. As a result of these studies, efforts are underway to assess antenatal corticosteroids and the late preterm infant (34 weeks to 36 weeks of gestation). Recent data show that the late preterm infant suffers increased morbidity and mortality compared to term fetuses, a situation that increases NICU admissions. Although their risk of respiratory distress syndrome is minor, late preterm infants are at high risk for other respiratory morbidities related to clearing fetal lung fluid. There is biological plausibility as to why steroids may be useful in this group; however, there is no evidence on which to base such a practice. A randomized, double-blinded, placebo-controlled trial was recently approved within the Network to evaluate whether steroids are helpful to improving outcomes of late preterm infants.

Technological Advances

Sometimes, and not just within obstetrics, new technology is developed and adopted without rigorous studies to confirm its efficacy and safety. With its more than 140,000 deliveries per year, the MFMU Network provides a unique opportunity to rigorously test obstetrical technology. For instance, the FDA approved the OxiFirst™ Fetal Oxygen Saturation Monitoring System in May 2000. This technology, fetal pulse oximetry, measures fetal oxygenation throughout labor and was marketed as an adjunct to conventional electronic fetal heart rate monitoring. Results of a randomized clinical trial by the manufacturer, published in 2000, showed that this technology reduced the cesarean delivery rate for fetal distress by 50 percent, but the rate of cesarean for dystocia doubled. FDA approval was contingent upon additional studies to examine the system's effectiveness and influence on cesarean delivery rates. An additional, larger study was also needed to assess infant outcomes in the event that an obstetrician withheld cesarean delivery in the presence of an abnormal heart rate pattern because fetal oxygenation was deemed normal.

The 14 clinical centers in the MFMU Network developed a research protocol under an Investigational Device Exemption to more definitively measure how the additional knowledge of fetal oxygen saturation impacts labor management and infant outcomes. A total of more than 5,300 nulliparous women were randomized at the time of delivery to either "open"—in which fetal oxygen saturation values were displayed to the clinician—or "masked"—in which the data was not available to the clinician. Results of the trial indicated no significant differences in cesarean delivery rates or infant outcomes between those deliveries for which obstetricians had fetal oximetry data versus those for which no oximetry data was available. This trial confirms the value of rigorous assessment of new technology.

A Spirit of Trans-NIH and Trans-Agency Collaboration

As the PPB-supported MFMU Network has grown and developed, additional expertise and funding for large studies has come from other NIH Institutes and federal agencies. For example:

- The MFMU Network is collaborating with the NINDS on a randomized trial of the beneficial effects of antenatal exposure to magnesium sulfate for the prevention of cerebral palsy. This trial design was based on case-control studies that identified magnesium sulfate as protective against the development of cerebral palsy. This double-blind, randomized trial involved 2,241 women at high risk of delivering very preterm (less than 32 weeks of gestation). Clinicians conducted more than 5,700 neurological exams and achieved 95.6 percent followup. The two-year follow-up period ended in 2007. The trial concluded that magnesium sulfate did not reduce the rate of the primary outcome of moderate to severe cerebral palsy or death, perhaps because death was the predominant component of the outcome. However, it did reduce the rate of moderate to severe cerebral palsy alone by 50 percent. Results were presented at the SMFM meeting in 2008. The manuscript was published in the *New England Journal of Medicine* in August 2008.
- The NHLBI provided funding to the MFMU Network to conduct the Combined Antioxidant and Preeclampsia Prediction Study (CAPPS) for the prediction and prevention of preeclampsia. This randomized, controlled trial is designed to determine if antioxidants (vitamins C and E) can prevent preeclampsia in low-risk women (n = 10,000). In addition, the observational component of the trial is designed to identify markers that may predict preeclampsia. Initiated in 2003, CAPPS recently completed enrollment, screening more than 30,000 women and enrolling in 10,000 patients in the randomized controlled trial and more than 2,300 in the observational cohort. Efforts are underway to determine which markers should be evaluated. The last deliveries are anticipated in November 2008. The Network expects to present the results at the annual SMFM meeting in 2009.
- In 2007, as the result of a congressional mandate requiring doctors to use quality measures to report on their performance, the MFMU Network collaborated with colleagues at the Agency for Healthcare Research and Quality to design a new study, *An Observational Cohort Study to Evaluate Measures of Quality of Obstetric Care*. The aim of this study is to identify several measures for assessing the safety of obstetrical care that can be incorporated into medical practice. The overall objective is to find tools for evaluating the quality of obstetric care by determining which process measures are associated with risk of poor outcomes. The five outcomes to be utilized are: uterine hemorrhage, maternal infection, thromboembolism, maternal third- and fourth-degree lacerations, and neonatal adverse outcomes. The study will include 25 hospitals from the Network. A recently completed pilot study of approximately 2,500 patients prospectively collected data related to these measures; this pilot resulted in changes to the data-collection tool. Network researchers anticipate that the study will collect data from more than 120,000 patient charts that will be abstracted over 12 months. To date, more than 6,500 charts have been abstracted.

The MFMU Network is working to release datasets from completed studies and trials in a format accessible to the public; that is, removing all identifiers. Two datasets have already been released and are available: Obstetrics Determinants of Neonatal Survival, and Preterm Prediction Study. Other datasets are also being prepared for release.

The MFMU Network Data Coordinating Center was recompeted in 2008; the clinical sites will be recompeted in 2011; more information on the MFMU Network is available at http://www.bsc.gwu.edu/mfmu/.

INFANT FEEDING PRACTICES STUDY (IFPS) II

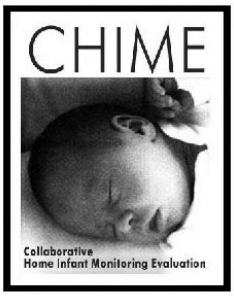
The IFPS II, a longitudinal survey of a large cohort of 4,900 women enrolled prenatally, was conducted collaboratively by the FDA, CDC, and the NICHD. Investigators followed more than 2,000 women through the first year of their infants' lives to assess a wide range of topics related to infant feeding practices, including postpartum depression, consumption of herbal and alternative medicines, breast pump use, and infant sleeping arrangements. The first set of 13 resulting papers includes results on several feeding issues: breastfeeding patterns, intensity, and duration; reasons for stopping breastfeeding; transitional and complementary feeding; provision of iron-rich foods and supplements to breastfed infants; the association between maternity care practices for the delivery location and the breastfeeding-related options associated with place of employment; infant formula handling practices; infant sleeping arrangements; food-related health problems, including food allergy; the effects of breastfeeding intensity, infant-initiated bottle emptying, and mothers' encouragement of bottle emptying on excess weight during infancy. These papers were published in a supplement to *Pediatrics* (Vol. 122 [Suppl], 2008).

Some of the major findings from the IFPS include the following:

- Researchers found a large variation from common advice on breastfeeding practices, such as the length of feeds and feeding from both breasts, and a small percentage of breastfeeding mothers (about 6 percent) who never put the baby to the breast.
- Nearly half of breastfed infants were supplemented with infant formula in the hospital, although this practice was not necessarily based on medical need.
- Nearly half of infants were fed solid foods before the age of four months; more than half of infants consumed foods high in fat or sugar at one year of age.
- About 58 percent of mothers who breastfeed their infants did not follow recommendations for adequate iron supplementation.
- One-quarter of the three-month-old infants were not placed on their backs to sleep as recommended; bed sharing was also quite common, reported by 34 percent of mothers with three-month-old infants.
- Among the various strategies mothers used to combine breastfeeding and employment, feeding the baby directly from the breast during the work day, either alone or in combination with pumping milk, was associated with longer breastfeeding duration after return to work.
- More than 20 percent of infants were reported to have a food-related health problem, with about 6 percent having an apparent food allergy. The majority of affected infants developed food-related health problems by six months of age.

The datasets from IFPS II will be available at http://www.cdc.gov/ifps/index toward the end of 2008; the scientific community can use these data to pursue additional analyses and research.

COLLABORATIVE HOME INFANT MONITORING AND EVALUATION (CHIME) STUDY



The CHIME Study, now complete, was a multi-center, cooperative study of home monitoring of high-risk infants. Almost 1,200 infants were enrolled in the following subject groups: healthy term infants, preterm infants weighing less than 1,750 grams, and siblings of babies who died of SIDS or who experienced an idiopathic apparent life-threatening event.

The PPB is now working to maintain the CHIME and NISP datasets (see the *SIDS Research: Risk Reduction* section of this report for more information on NISP) and to facilitate access to the data by the scientific community, thus ensuring that these important data are used to their fullest extent. To do so, the Branch funded the CHIME Data Coordinating and Analysis Center in fiscal year 2004 to complete the following tasks:

- Determine the factors and physiological processes that predict extreme cardiorespiratory events, including early antecedents, developmental patterns, and immediate characteristics of onset and recovery. These analyses may include comparisons that distinguish "extreme" versus "conventional" events, when appropriate.
- Continue the NISP Study and evaluate trends in infant sleep practices and dissemination of the *Back to Sleep* recommendations, and the factors that influence these trends. The Center will make efforts to increase the proportion of minorities in the completed calls, while using the current list sample.
- Facilitate scientific community access to the data collected by the CHIME and NISP Studies.

As explained earlier, NISP interviews were conducted annually from 2003 to 2007; the NICHD and AAP used the data to guide *Back to Sleep* campaign activities and to follow the impact of the 2005 AAP recommendations on bed sharing and pacifier use. Overall, 5,549 respondents, including an enhanced sample of caretakers with lower education background, were interviewed by phone during the five-year study period (5,701 infants). Interviews were also conducted in Spanish.

The CHIME/NISP Web site, http://dccwww.bumc.bu.edu/ChimeNisp/, was established in 2004 as the primary portal to these datasets. During the project period, there have been more than 20,000 visits on the site from more than 4,000 different Internet Provider addresses. The rate of visits has steadily increased, with number of visits in the current year approximately twice that of the prior year. The Data Coordinating Center has fielded 52 inquires from investigators regarding the datasets.

Currently, two investigator-initiated grants are funded to analyze the CHIME dataset:

- Grant Number: 1 R01 HD045653-01; PI: Robert A. Darnall, M.D., Project Title: *Spontaneous Arousals in "CHIME" Infants at Risk for SIDS*
- Grant Number: 1 R03 HD42479-01 (Revised); PI: Stephanie A. Schuckers, Ph.D., Project Title: *Predicting Life-Threatening Events in CHIME Infant Data*

The CHIME database, which includes all raw physiological records and study forms was also recently transferred to CD-ROM.

MATERNAL-FETAL SURGERY NETWORK

In 2001, the PPB created the Maternal-Fetal Surgery Network to evaluate, using a randomized clinical trial, *in utero* surgery as a treatment for antenatally diagnosed spina bifida. The Management of Myelomeningocele Study (MOMS) trial includes three sites: Children's Hospital of Philadelphia, Vanderbilt University Medical Center, and the University of California, San Francisco. The PPB provides additional oversight and guidance, and the George Washington Biostatistics Center serves as the Data Coordinating Center for the Network.

This collaborative, multi-center trial is comparing the safety and efficacy of fetal surgical repair to traditional postnatal repair of open neural tube defects. Of the 200 women planned for enrollment, 145 were randomized into the study as of July 2008. For more information on the MOMS trial or on the Maternal-Fetal Surgery Network, visit http://www.spinabifidamoms.com/english/index.html.

VAGINAL ULTRASOUND CERCLAGE TRIAL

As explained in the earlier section about the MFMU Network, prior studies demonstrated that the presence of a short cervix significantly increases the risk of preterm delivery; however there is no consensus or scientific evidence on the proper clinical management of this situation. The Vaginal Ultrasound Cerclage Trial (1U01HD039939-01A1; PI: John Owen, M.D.) is a multi-center, randomized clinical trial designed to determine the efficacy of cerclage (a purse-string suture placed around the uterine cervix) for the prevention of spontaneous preterm birth prior to 35 weeks' gestation. Researchers at 11 centers studied women at significant risk for recurrent spontaneous preterm birth (e.g., those with a prior spontaneous birth at 17 weeks' to 33 weeks' gestation) and those at increased risk based on mid-trimester ultrasonographic findings of a cervical length less than 25 mm. This procedure is currently one of the most controversial issues in obstetrics and maternal-fetal medicine. Enrollment of the total sample size of 300 women is complete. Results from this trial, anticipated in early 2009, will provide significant evidence for the specialty, for women, and for their pregnancies.

COMMUNITY CHILD HEALTH RESEARCH NETWORK (CCHN)

The CCHN is a community-linked research effort about maternal and child health that relies on cooperative agreements to plan and perform a multi-site, multi-level study examining how community, family, and individual influences interact with biological influences to result in health disparities in pregnancy outcomes and in infant and early childhood mortality and morbidity. One of the foci of the research enterprise is to improve family heath in the

interconceptional period as a means of improving the outcomes of future pregnancies. The CCHN includes five collaborating sites, each one a partnership between an academic institution and community institutions; staff from the PPB, from the NICHD Demographic and Behavioral Sciences Branch, and from the NINR are also active in this effort. The CCHN has made progress toward its core hypotheses, methods development, and study design.

The Phase I goal of the research program is to blend substantive theory, measurement regimes, and study designs currently found in the biomedical, social, and behavioral sciences into a study of infant mortality and child health. The current products of Phase I include a plan of action describing the hypotheses, design, and content the study, as well as preliminary work from each site that will provide a foundation upon which to build such a research network. Findings garnered from this study will improve understanding of the complicated interplay among environmental and genetic factors that produces biological outcomes in high-risk minority populations.

PRENATAL ALCOHOL IN SIDS AND STILLBIRTH (PASS) NETWORK

In 2003, the NICHD and NIAAA funded cooperative agreements to establish Phase I of the PASS Network, the primary hypothesis of which is that prenatal alcohol exposure increases the risk for SIDS and stillbirth. The conceptual framework that underlies the proposed studies is that the interaction among different environmental and genetic factors affects the risk for a spectrum of disorders, including SIDS, stillbirth, and the early manifestations of fetal alcohol syndrome and fetal alcohol spectrum disorders, related to prenatal alcohol exposure from mid-gestation through infancy.

The Network is composed of two comprehensive clinical sites at the University of South Dakota and Stellenbosch University, South Africa; a developmental biology and pathology center at Children's Hospital, Boston; a Data Coordinating and Analysis Center at DM-STAT; and a physiology assessment center at Columbia University.

During Phase I, researchers conducted a pilot study to demonstrate the feasibility of collecting alcohol exposure, psychosocial, and physiological data from mothers, fetuses, and infants prospectively throughout the prenatal, perinatal, and postnatal periods. The target enrollment for the prospective study was 380 women, and 579 were enrolled. The Phase I data on drinking patterns during pregnancy in the catchment populations confirmed the expected high exposures and enabled researchers to develop samples sizes for Phase II.

The Network also conducted retrospective studies of stillbirths and SIDS to determine feasibility of diagnostic procedures—those to collect and analyze brain tissue and other relevant specimens from stillbirths and post-discharge infant deaths, and those for interviewing the mothers. All targets for enrollment and specimen collection were met.

In 2006, the PASS Network successfully competed for Phase II. Its study will be the first longitudinal effort, beginning in the prenatal period, to examine the effects of fetal alcohol exposure on fetal and infant morbidity and mortality. The PASS Network has the opportunity to

gain new knowledge about genetic-environmental interactions that influence prenatal alcohol toxicity; the direct effects of prenatal alcohol exposure on the human brain and placenta, as well as on autonomic and neurological behaviors in early human life; the potential links between SIDS and unexplained stillbirth; and the effects of prenatal alcohol exposure on the risk for perinatal and infant mortality. The findings also have the potential to help develop innovative ways to predict and/or prevent the adverse effects of prenatal alcohol exposure before and at birth.

STILLBIRTH COLLABORATIVE RESEARCH NETWORK (SCRN)

Stillbirth, defined as death at 20 weeks' gestation or greater, accounts for a large proportion of perinatal mortality. According to annual national vital statistics, the number of fetal deaths at 20 weeks' or more gestation, including stillbirths, is similar in magnitude to the total number of infant deaths in the United States. To begin to address gaps in knowledge about stillbirth, the PPB issued *Research on the Scope and Causes of Stillbirth in the United States* (RFA-HD-02-025) to create a Network of clinical research sites, with a central data collection and analysis resource, for developing and implementing common research protocols to study stillbirth. The awards for the SCRN were made in September 2003 to the following clinical investigators and research sites:

- Dr. Marshall Carpenter, Women and Infants Hospital of Rhode Island, Providence;
- Dr. Donald Dudley, University of Texas Health Sciences Center, San Antonio;
- Dr. George Saade, University of Texas Medical Branch, Galveston;
- Dr. Robert Silver, University of Utah, Salt Lake City;
- Dr. Barbara Stoll, Emory University, Atlanta; and
- Dr. Corette Parker, Statistical Center at RTI International, Raleigh.

In the first year, the Network developed a multi-site, population-based, hypothesis-driven, case-control study with prospective enrollment of stillbirths as cases and live births as controls. Hypotheses were developed in surveillance and epidemiology, fetal and placental pathology, maternal disease mechanisms, immunology and infectious diseases, and genetics; these hypotheses have driven the design requirements of the study, including case ascertainment; selection, number, and type of controls; and timing and approach to data collection and management. Following the development of the study design, hypotheses, protocol and research instruments, and the piloting phase of the study, Network researchers began recruitment of cases and controls.

To date, 58 hospitals are participating in the SCRN protocol. The final sample size for the study is 700 cases of stillbirth, 500 cases with complete information including autopsy, and 1,850 controls. This sample size was selected to assure at least a 1:1 ratio of live births to stillbirths across ethnic categories and GA. Enrollment was completed in September 2008. The information derived from this five-year study will benefit families who have experienced a stillbirth, women who are pregnant or who are considering pregnancy, and their physicians. In

addition, the knowledge will support future research aimed at improving preventive and therapeutic interventions and at understanding the pathological mechanisms that lead to stillbirth.

GENOMIC AND PROTEOMIC NETWORK FOR PRETERM BIRTH RESEARCH (GPN/PBR)

The main objective of the GPN/PBR, established in 2005, is to use wide-scale, high-output genomic and proteomic strategies to accelerate knowledge of the mechanisms responsible for spontaneous preterm birth. Approaches, such as genome-wide scans and global serum protein profiling, are used to identify new biomarkers, which increase the risk or are predictive of a spontaneous preterm birth, and to use this information for understanding the molecular mechanisms involved. In addition, the Network acts as a resource for the scientific community by freely providing genomic and proteomic data generated by its research for secondary analyses.

Network projects consist of three collaborative core components: the clinical core, comprising three clinical sites (University of Alabama at Birmingham, University of Texas at Galveston, and University of Utah), which is responsible for subject recruitment and specimen collection; the analytical core (University of Pennsylvania), which is responsible for genomic and proteomic analyses; and the data management, statistics, and informatics core (Yale University), which is responsible for central data collection, analysis, and management. Three study designs, explained below, were developed and recruitment for these studies began in late 2007.

- The first study will follow 500 women at high risk for preterm birth (e.g., previous spontaneous preterm birth) throughout pregnancy, starting in the first trimester. The primary purpose of this study is to establish a simple test, using blood, urine, or saliva, to detect a biomarker for predicting whether a woman will have a spontaneous preterm delivery. If successful, this test would allow an intervention to be introduced early enough to possibly prevent the preterm delivery.
- The second study will recruit 1,000 women who deliver spontaneously preterm and 1,000 women who deliver spontaneously at term. Researchers will collect a DNA specimen from each woman to determine a DNA profile that increases the possibility for a spontaneous preterm birth. If successful, this study would enable physicians to determine women's susceptibility to a preterm birth even before conception. This information would also allow physicians to closely monitor their patients and introduce the appropriate intervention based on a particular DNA profile. DNA from the newborn will also be obtained and may be used to develop a profile for predicting the outcomes of a preterm infant.
- The third study will recruit 80 women, in labor and not in labor, for a medically indicated caesarean section resulting in either a spontaneous preterm or term delivery. This effort will include an ancillary study of an additional 40 women, in labor and not in labor, whose deliveries are complicated by the pPROM, and who undergo a medically indicated caesarean section. Numerous delivery specimens will be collected for analysis. This study is a very detailed global analysis of DNA, RNA, and protein expression. A comparison of the analyses between the various groups of women should allow important insight into the molecular mechanisms involved in spontaneous preterm birth and pPROM.

Researchers anticipate that recruitment of subjects for these three studies will be complete by late 2009, and that the final analyses will be completed by late 2010. Ultimately, this research may lead to relatively simple screening tests to identify pregnant women (or possibly even women contemplating pregnancy) who are at risk for a spontaneous preterm birth and provide them with interventions, which may enable them to carry a pregnancy to term. Furthermore, the selection of a particular intervention (therapy) may be informed by an individual's genetic or proteomic profile.

BRANCH ACTIVITIES: TRAINING AND CAREER DEVELOPMENT PROGRAMS

The Branch supports research training and career development through various award mechanisms. For fiscal year 2004 through fiscal year 2007, the PPB funded the following training and career development awards:

- Two new and five continuing National Research Service Award (NRSA) Predoctoral Fellowships for Minority Students and Students with Disabilities (F31); of a total of six applications, two were funded, resulting in a 33-percent success rate.
- No new and two continuing NRSA for Individual Postdoctoral Fellowship (F32); of the 16 applicants, none were funded, resulting in a 0-percent success rate.
- Four new and 15 continuing Mentored Clinical Scientist Development Awards (K08); of the 14 fourteen applicants, four were funded, resulting in a 29-percent success rate.
- Five new and 12 continuing Mentored Patient-Oriented Research Career Development Awards (K23); of the 17 applicants, five were funded, resulting in a 29-percent success rate.
- One new and four continuing Mid-Career Investigator Awards in Patient-Oriented Research (K24); of the three applications, one was funded, resulting in a 33-percent success rate.
- Four new, seven renewals, and five continuing NRSA Institutional Research Training Grants (T32); six of these grants have been active for more than 20 years. Of the 20 applicants, 11 were funded, resulting in a 55-percent success rate.

It is noteworthy that neonatal/perinatal fellows and postdoctoral scientists funded through the Branch's T32 mechanism have been presenting scientific papers in large numbers at regional and national professional society meetings. The Branch has tracked these data since 2005; each year these grantees present 45 to 50 research papers at the annual meetings of the Pediatric Academic Societies alone.

OTHER BRANCH ACTIVITIES

INSTITUTE OF MEDICINE (IOM) PREGNANCY WEIGHT GUIDELINES

The PPB is co-sponsoring this IOM activity, which will review and update the 1990 IOM recommendations for weight gain during pregnancy. The new report will also suggest ways to encourage adoption of these recommendations through consumer education, strategies to assist practitioners, and public health outreach. The committee is sponsored by the Health Resources and Services Administration, NIH (NICHD, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Nutrition Research Coordination), CDC, DHHS Office of Women's Health, and the March of Dimes. The committee report is expected by summer 2009.

BEST PHARMACEUTICALS FOR CHILDREN ACT (BPCA)

The congressional mandates of the BPCA provide an opportunity to address the challenges of conducting drug-related clinical trials in children for the purpose of labeling drugs for use in pediatric populations. Branch staff, especially Drs. Tonse Raju and Rosemary Higgins, are actively involved in this important initiative, in collaboration with other NICHD and NIH staff.

Drs. Raju and Higgins helped to organize an NICHD/FDA Newborn Drug Development Initiative to foster the development of safe and effective drug therapies for term and preterm infants. Branch staff continue to be involved in BPCA activities in conjunction with the Obstetric and Pediatric Pharmacology Branch within the NICHD Center for Research for Mothers and Children.

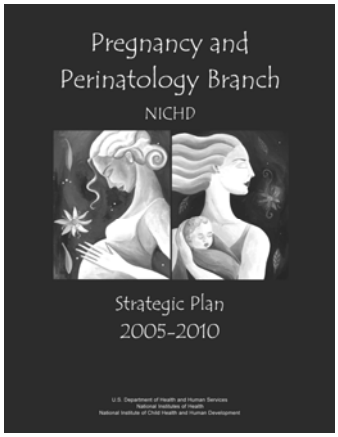
DHHS INTERAGENCY COORDINATING COUNCIL ON LOW BIRTH WEIGHT AND PRETERM BIRTH AND DISPARITIES SUBCOMMITTEE

The purpose of this Interagency Coordinating Council is to galvanize multidisciplinary research, scientific exchange, policy initiatives, and collaboration among DHHS agencies, including the NIH, and to assist the Department in focusing efforts to achieve the greatest advances toward the national goal of reducing infant mortality. The challenges faced by the Council include assuring adequacy of data, uncovering new knowledge through research, and promoting the best possible delivery and financing of relevant health care. In particular, the DHHS Secretary asked the Council to develop a Department-wide research agenda on combating low birth weight and its associated outcomes.

This Council made recommendations related to DHHS research on preterm birth, low birth weight, and SIDS. In the area of preterm birth, opportunities for future research included mechanisms of initiation of labor and role of infection with respect to preterm delivery. For low birth weight, areas of research included smoking cessation, improvement of ultrasound dating to reduce unintentional preterm or low birth weight induction or delivery, investigation of ways to discourage assistive reproductive technology practices leading to multiple gestation, and investigation of partnerships for research. The Council also recommended assistance with approval of 17-OHPC to make it available for physicians to use in evidence-based practice. Suggestions for meetings, including *Caesarean Section on Maternal Request* and *The Prevention of Preterm Birth*, were recommended by the Council. In the area of SIDS, the Council recommended studies on the impact of prenatal alcohol use by American Indians/Alaska Natives

on SIDS rates and possible interventions. Recommendations for continued research into the mechanisms involved in SIDS were made, as well as those for continued efforts of the *Back to Sleep* campaign to reduce the rates of SIDS.

FUTURE DIRECTIONS FOR THE PPB



On December 5-6, 2002, the Branch convened a two-day workshop to develop a research agenda that would help guide Branch activities and set priorities for the years 2005 through 2010. The findings from this two-day workshop were used to develop the Pregnancy and Perinatology Branch Strategic Plan: 2005-2010. The plan included ongoing areas of PPB-supported research and outlined some steps for expanding these initiatives. The plan also identified new areas of emphasis crucial to the PPB mission. New areas of emphasis included:

- Prematurity
- Fetal development, including maturation of individual organ systems and the impact of interventions on long-term function
- Maternal morbidities
- Neonatology, specifically intensive-care and long-term outcomes
- Fetal/neonatal brain development and damage, including prenatal, perinatal, neonatal, and infant periods
- Training of scientists and physician-scientists
- Defining and improving the link between fetal, obstetric, and neonatal interventions and infant/child outcomes

Since the development of the plan, the Branch has undertaken many activities to specifically address issues raised as high priorities. Branch staff have encouraged applications in the areas of emphasis. Although the time since development of the plan has been one of fiscal constraint, the PPB has initiated a number of initiatives to address the topics listed above. Future areas of research emphasis include many topics identified in the plan because many of the areas are broad and will require sustained efforts over decades to make inroads.

On April 21, 2008, in accordance with the NICHD's process for improving the transparency of and enhancing input toward strategic planning, the Branch convened an expert panel to review its activities and formulate future directions. The expert panel, comprising members of the NACHHD Council, professionals with backgrounds in neonatology, pediatrics, obstetrics, maternal-fetal medicine, and epidemiology, and representatives from interested public groups (see Appendix G for a list of panel members), identified the most important scientific opportunities that the Branch should consider pursuing during the next four years, including and emphasizing those areas that are making the most rapid advances, those that need special actions or stimulation by the Branch, and those that are not currently represented in the portfolio. An overarching theme of the panel's discussion was that, for all areas, understanding the mechanism(s) of disease, including basic and translational research, is critical.

PANEL DISCUSSION

The panel highlighted five critically important scientific opportunities.

Obesity and nutrition and how these features affect the mother, the developing fetus, and the child were described as among the most important scientific opportunities for the Branch. Panel members suggested that such research include the pre-pregnant obese woman, weight gain during pregnancy, and the lifetime impact of post-pregnancy obesity. In addition, panel members noted the importance of understanding the effects of maternal obesity on the fetus; for instance, members cited a lack of knowledge about hypoglycemia in newborn, long-term impacts on the baby, and when intervention is required.

The Branch indicated its desire to stimulate this area of research with a Request for Applications (RFA), which would include the treatment and management of obesity in pregnancy. In addition, the Branch plans to hold a workshop on optimizing nutrition in the NICU and would continue to support the IOM in updating its pregnancy weight gain guidelines report. The Branch also intends to capitalize on the findings from its researchers to stimulate new research in this area and to support trans-NIH conferences highlighting these issues.

Preterm labor and preterm delivery remain a predominant scientific opportunity for the Branch and represent the primary cause of neonatal mortality with significant short- and long-term morbidities for those who survive. To date, the Branch's focus has been on spontaneous preterm birth. The panel felt it was important to shift the focus to understand what is causing the increase in preterm birth rates and to evaluate other subgroups, such as late preterm births, and the care (medical and behavioral-based care) of the preterm infant.

The Branch plans to stimulate this area by emphasizing the outcomes from a workshop held on this topic and from the recent *Surgeon General's Conference on the Prevention of Preterm Birth.* The Branch will continue to support and encourage studies on the management of the preterm infant, especially through the NRN, and hopes to initiate a study on nulliparous women that will enhance understanding of preterm birth in another subgroup with a large and growing rate of preterm births.

Long-term effects of pregnancy (fetal origins of adult disease) and the concept that what occurs during pregnancy may predict long-term maternal health was highlighted as another major opportunity for the Branch. This area would include pregnancy as a risk factor of later cardiovascular disease, as well as the fetal perspective; that is, understanding how the intrauterine environment impacts the long-term health for the child and its trans-generational effects.

The Branch strongly believes that improving pregnancy and pregnancy outcomes will result in improved life-long health for the nation. The Branch will encourage investigators to research this area and will readily partner with other Institutes and agencies to stimulate the field.

Development of non-invasive methods for evaluating the fetus and placenta *in utero* was also highlighted as an area of significant scientific opportunity for the Branch. The ability to better evaluate the fetus and placenta from early pregnancy, using non-invasive methods, is critically needed to facilitate understanding of growth and development. The panel also suggested pushing the technologies beyond ultrasound and Doppler, using such technologies as magnetic resonance spectroscopy, fetal DNA, and fetal RNA to create more accurate assessments of fetal growth.

The Branch plans to work with other Institutes, such as the National Institute of Biomedical Imaging and Bioengineering, and agencies, such as the FDA, in order to move this area forward.

Placental and fetal growth and development was also identified as a major opportunity for the Branch. Research needs highlighted included transplacental passage, physiology, pharmacology, environmental exposures, genomics, and epigenetics. Further understanding of the placenta, as well as its functions, and linking studies of the placenta to vascular biology and placental regulators would also be critical for the Branch to pursue.

The Branch plans to issue a PA to stimulate research ideas in the field of epigenetics. In addition, the Branch will continue to work with the funded researchers who responded to the RFA on fetal growth restriction to encourage collaborative research in these fields.

Other areas also highlighted as major opportunities for the Branch include:

- Markers for adverse pregnancy outcome in the nulliparous patient—a woman without known risk factors; most work to date has focused on women with known risk factors; an RFA was recently published to address this issue
- Short-term effects of pregnancy on physical and mental well-being of the mother; the Branch will continue to partner with NIMH on the PA related to women's mental health in pregnancy
- Effectiveness of prenatal care
- Ongoing disparities in health outcomes
- Evidence for intrapartum obstetrical care
- Evidence for resuscitation of the newborn
- Prenatal genetics/screening, including new technologies and deployment, such as disparities and health care utilization
- Population-based environmental (e.g., chemicals, toxins, viruses) exposures and long-term effects (e.g., ASDs, cerebral palsy, etc.); perinatal factors beyond genetics that contribute to autism spectrum disorders, schizophrenia, etc. (the completion of the human microbiome project may be useful in this work)
- Newly developed and developing technologies, including nanosystems therapy, for the tiny neonate and in regenerative medicine
- Nutrition for both the mother and the neonate, including optimal nutrition for the developing brain, the ability to impact brain development using nutrition (especially in vulnerable neonates such as the preterm infant and those with fetal alcohol syndrome), and the role of both micro- and macronutrients

- Management of substance abuse in pregnancy, including impact on pregnancy and neonatal outcomes and childhood, and the effects of other drugs, such as methamphetamines and selective serotonin reuptake inhibitors
- Social determinants of adverse pregnancy outcome

POSSIBLE BRANCH ACTIVITIES

The panel raised a number of concerns about ability to integrate training opportunities within the Branch priorities, including:

- The difficulties newly trained investigators face, coming off a K or T grant, trying to get an R grant: With the fiscal constraints at the NIH and the mission-based budgets at academic institutions, these investigators are being lost. The panel noted that if a mechanism could be developed to facilitate this transition, it would be very beneficial.
- The panel described a significant gender disparity in funded investigators, given that 40 percent to 60 percent of obstetricians and gynecologists are women.
- Members explained the importance of continuing support for an existing cohort of mentors. Given the burden on mentors to get their own grants funded and to mentor new investigators, the panel suggested a new grant mechanism for a joint mentor-mentee grant; the mechanism would be two linked grants (thus smaller than a program project) focused on single theme, but approaching it from different angles. Such a mechanism would help to ensure commitment of mentor, while also acknowledging mentors' role, and assisting the mentee in getting an R grant.
- In light of the five areas noted as scientific opportunities, the panel expressed a need for the Branch to support adequate training on bioinformatics and epigenetics.
- Members added that T32 recipients need to demonstrate that they have training expertise in the areas of high priorities.
- Grantees need to be able to train people in new techniques; however, the panel noted that no mechanism currently exists to allow for training in a new technique (e.g., short term, one to two months).
- Metrics for and monitoring of training program success were also identified as critical but currently lacking.
- The panel suggested that the field needed a national training program for perinatology, akin to the Physician-Scientist Development Program. Such a program could include training on how to do research and short-term training in specific techniques, mentoring, career advice, and professional development (possibly with nationwide mentors).
- Members suggested incorporating perinatology into the Clinical and Translational Science Award program in a manner similar to pediatrics; they noted that it is critical for human development be incorporated into this program.

The public health issues relevant to the Branch had a striking parallel to the important scientific opportunities. The public health issues most critical to address included:

- Obesity and nutrition
- Preterm labor and birth
- Fetal origins of adult disease
- Pandemic infections (including influenza) and the effects on pregnancy and pregnancy outcomes; although this work may affect a small segment of population, the impact on that population will be large
- Nulliparous patient—namely that what a woman does in the first pregnancy has life-long impacts, including those on future reproductive health and the long-term health of the mother
- Environmental exposures
- Intrapartum care and events, such as the ability to identify true versus false labor both in the term and preterm settings; when cesarean delivery is appropriate; the ability to identify a women who will have an uncomplicated vaginal delivery (the safest delivery method) versus those who will have complications or a cesarean

Other important public health issues included:

- Following children with chronic diseases (e.g., BPD, preterm infants, congenital heart disease) as they become adults
- Understanding pregnancy as a framework for future health
- Elucidating the mechanisms and effects of complications of pregnancy, such as GDM, pregnancy-induced hypertension, preeclampsia, and postpartum health, such as failure to lose weight postpartum, recovery from cesarean delivery in first pregnancy, and mental health issues (i.e., anxiety/depression); also learning about the effects of fetal growth restriction and macrosomia on long-term health
- Nutrition and availability of good nutrition, including the current food shortage due to gas prices
- Disparities in outcomes along racial/ethnic lines
- Social determinants of adverse pregnancy outcomes (the National Children's Study's household enrollment could provides a potential area for collaboration)
- Effect of assistive reproductive technologies on pregnancy outcomes and beyond

The panel also noted a need for the NICHD to motivate other Institutes to focus on pregnant women and neonates/children. One way to accomplish this task would be to highlight the public health issues and their implications on long-term health. The panel observed that the public health issues within the PPB portfolio are not considered to be general public health issues despite the work demonstrating how critical the pregnancy and perinatal timeframes are.

Members also focused on communication needs during the meeting, including the need to have initiatives/mechanisms to allow the dissemination of information about PPB-related public health issues to grantees and the public. One suggestion was for the PPB to develop an electronic newsletter, which could be sent weekly or monthly to all NICHD-funded investigators.

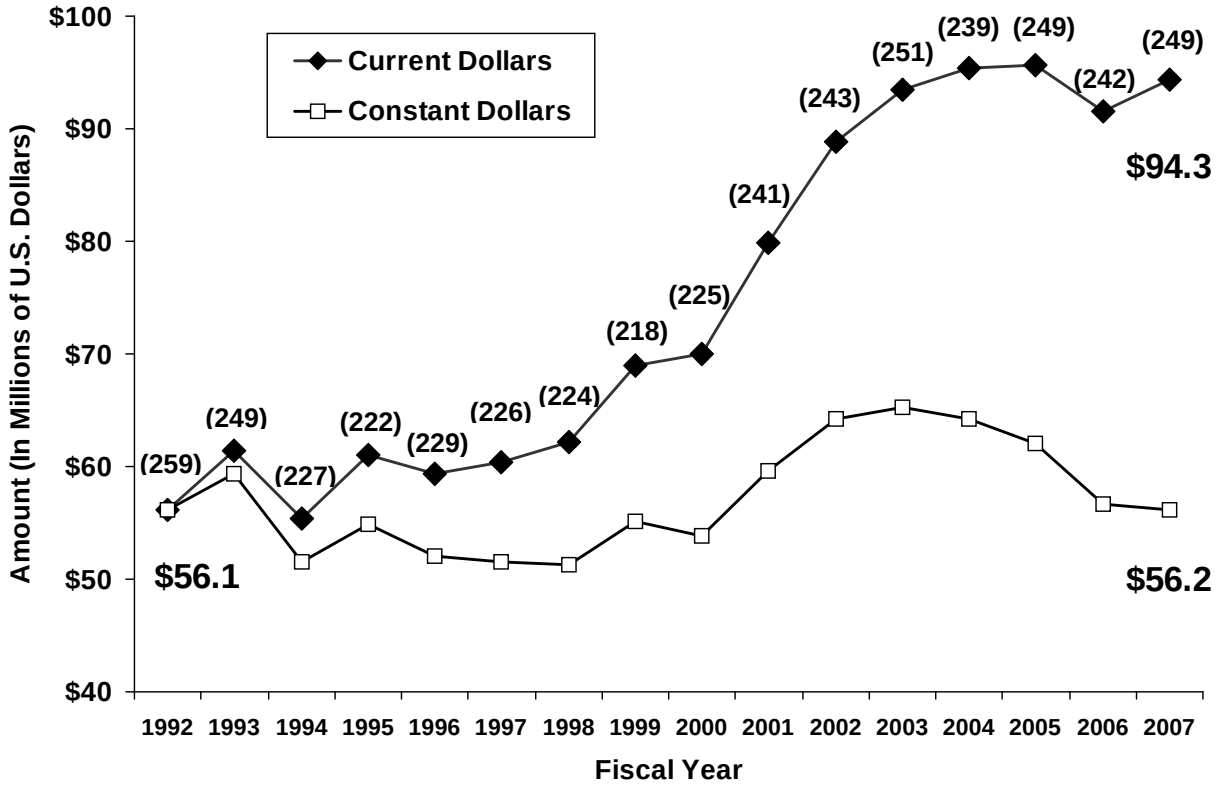
FIGURES AND TABLES

Please Note: The numbers and amounts presented in these figures and tables represent unofficial figures prepared by the NICHD Referral and Program Analysis Branch. Some of the amounts may differ from those reported by the NIH Research, Condition, Disease, and Categorization Process, which provides the only offical amounts for the NIH. Please visit http://report.nih.gov/rcdc to view offical numbers and amounts for specific disease categories.

TABLE 1: PPB PROJECTS BY PROGRAM AREA, FISCAL YEARS 2000, 2004, AND 2007

	Fiscal Year 2000		Fiscal Year 2003		Fiscal Year 2007	
	Projects	**Funds**	**Projects**	**Funds**	**Projects**	**Funds**
Maternal						
Basic	13	$2,866,387	7	$1,638,891	15	$3,921,172
Clinical	44	$17,069,455	33	$16,916,727	51	$21,523,533
Fetal						
Basic	33	$7,392,339	28	$7,414,627	35	$8,090,949
Clinical	4	$841,115	12	$4,592,060	16	$6,516,308
Placental	30	$5,833,037	38	$10,134,258	33	$8,272,131
Labor and Delivery	51	$13,264,197	53	$14,777,817	43	$12,757,772
Neonatal						
Basic	12	$1,921,424	11	$2,354,008	8	$2,375,736
Clinical	23	$9,927,268	40	$20,460,847	42	$16,207,690
SIDS						
Basic	16	$3,839,299	18	$4,325,465	18	$3,968,396
Clinical	15	$3,033,301	10	$3,300,173	14	$5,968,608
Subtotal:	241	$65,987,822	250	$85,914,873	275	$89,602,295
Training						
F31			4	$111,119	2	$76,974
F32	3	$116,988	4	$198,150		
T32	9	$1,254,514	11	$2,175,188	13	$3,152,451
Ks (01,02,08,12,23,24,25)	11	$2,615,354	26	$5,042,460	12	$1,504,979
Subtotal:	23	$3,986,856	45	$7,526,917	27	$4,734,404
Total:	**264**	**$69,974,678**	**295**	**$93,441,790**	**302**	**$94,336,699**

FIGURE 1: PPB GRANTS AND CONTRACTS IN CURRENT AND CONSTANT DOLLARS, FISCAL YEAR 1992 TO FISCAL YEAR 2007



(Note: Figures include total grant and contract extramural funding; numbers in parentheses represent the number of projects.)

FIGURE 2: PPB FUNDS BY PROGRAM CATEGORY, SELECT FISCAL YEARS

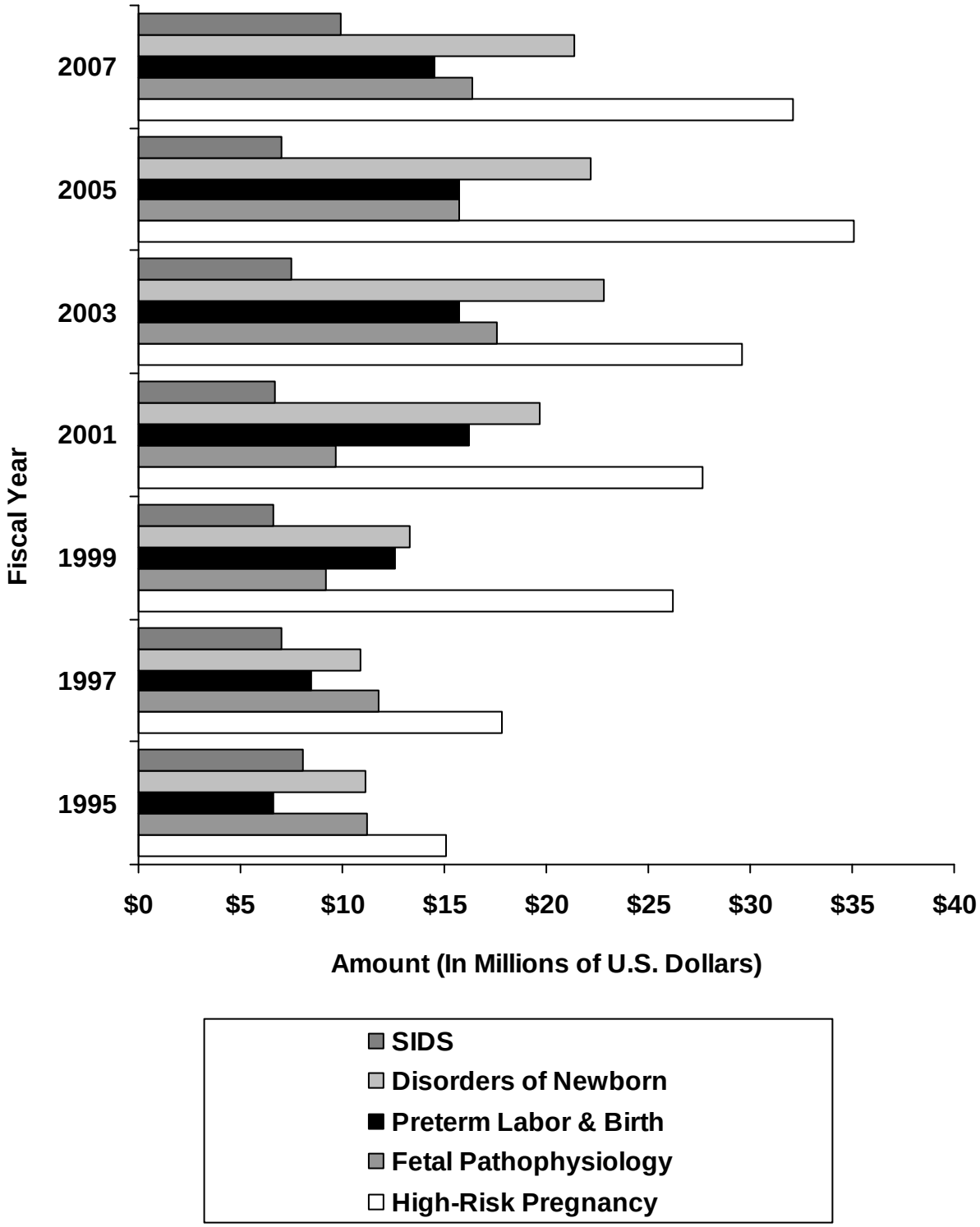


FIGURE 3: PPB-SUPPORTED RESEARCH BY DEPARTMENT, SELECT FISCAL YEARS

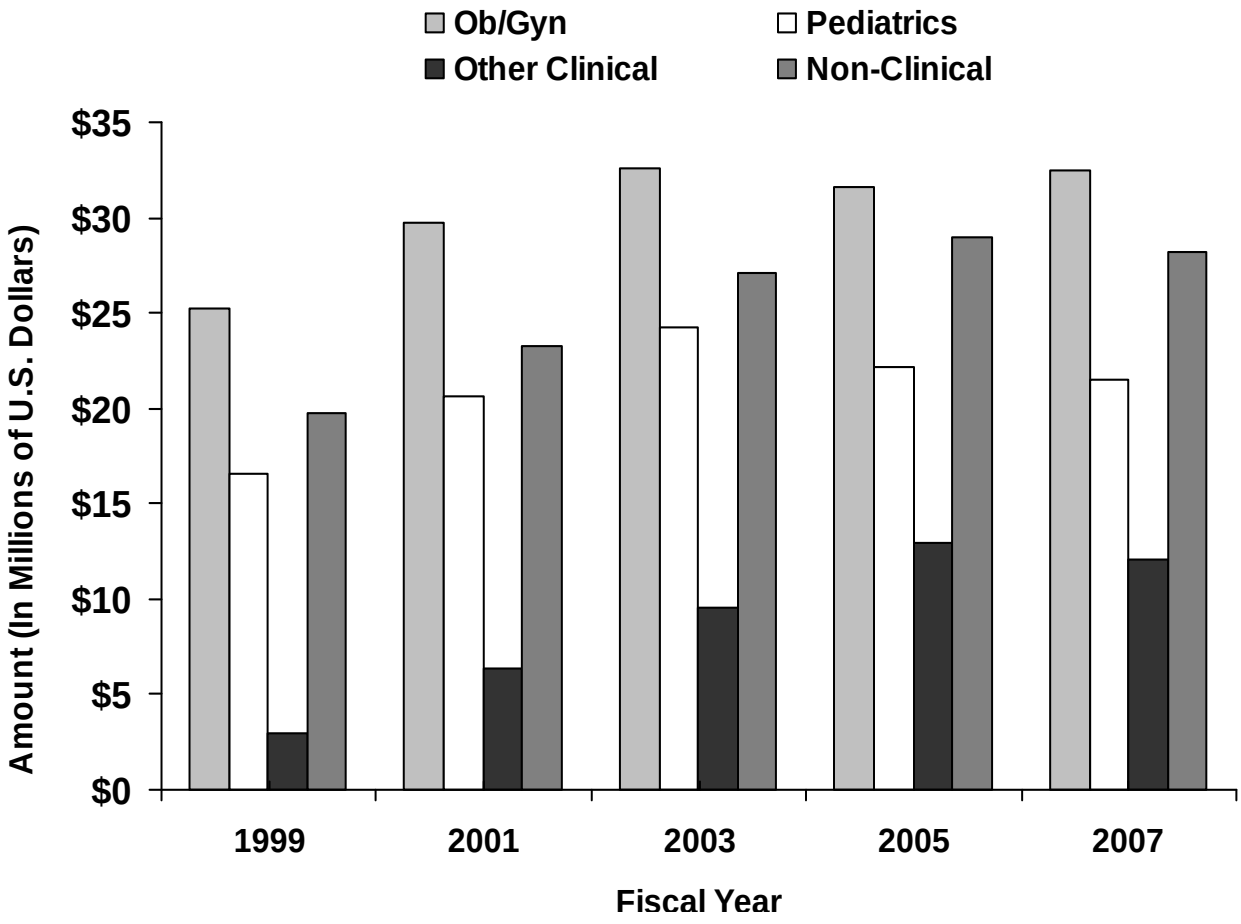


FIGURE 4: PPB-SUPPORTED RESEARCH BY INVESTIGATOR DEGREE, SELECT FISCAL YEARS

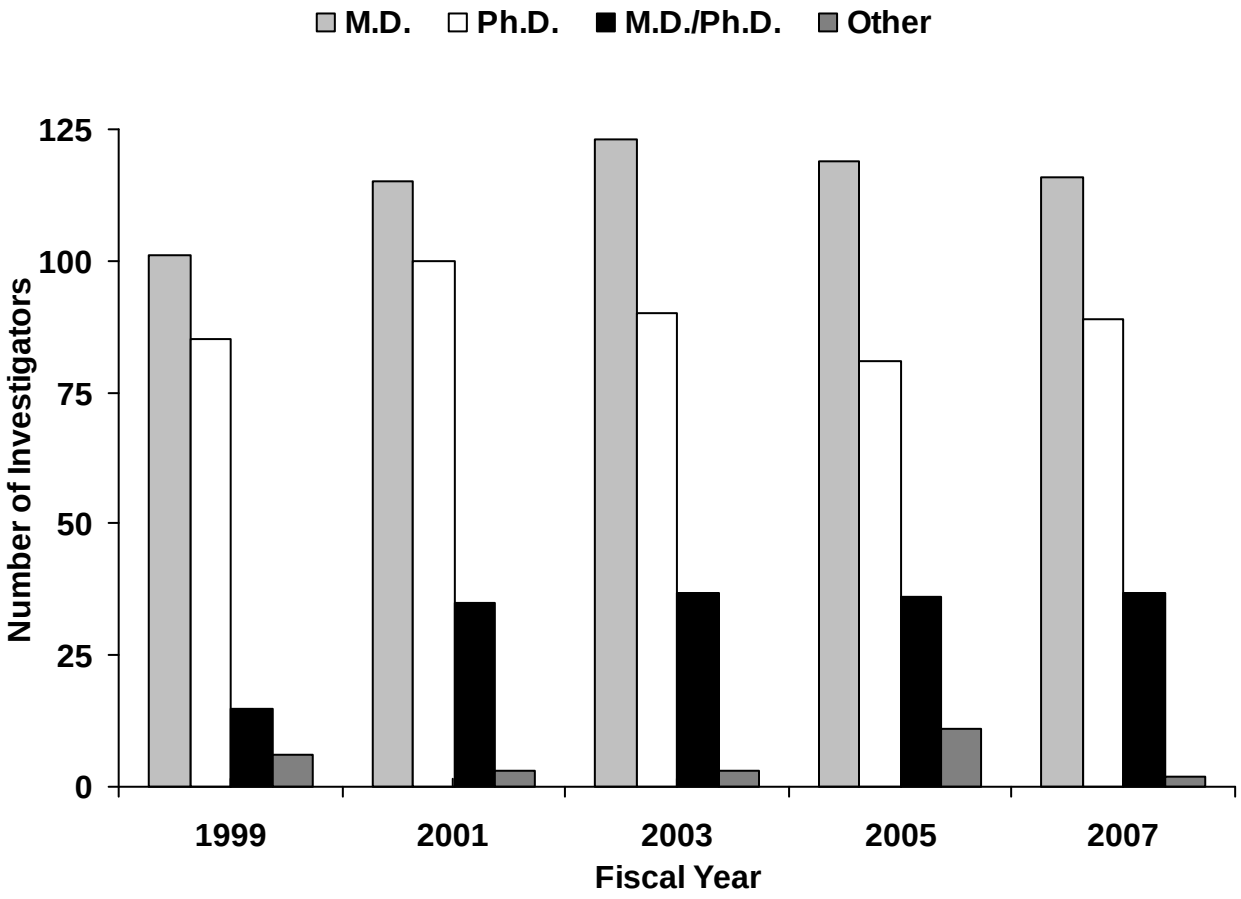


FIGURE 5: PPB-SUPPORTED RESEARCH BY INVESTIGATOR GENDER, SELECT FISCAL YEARS

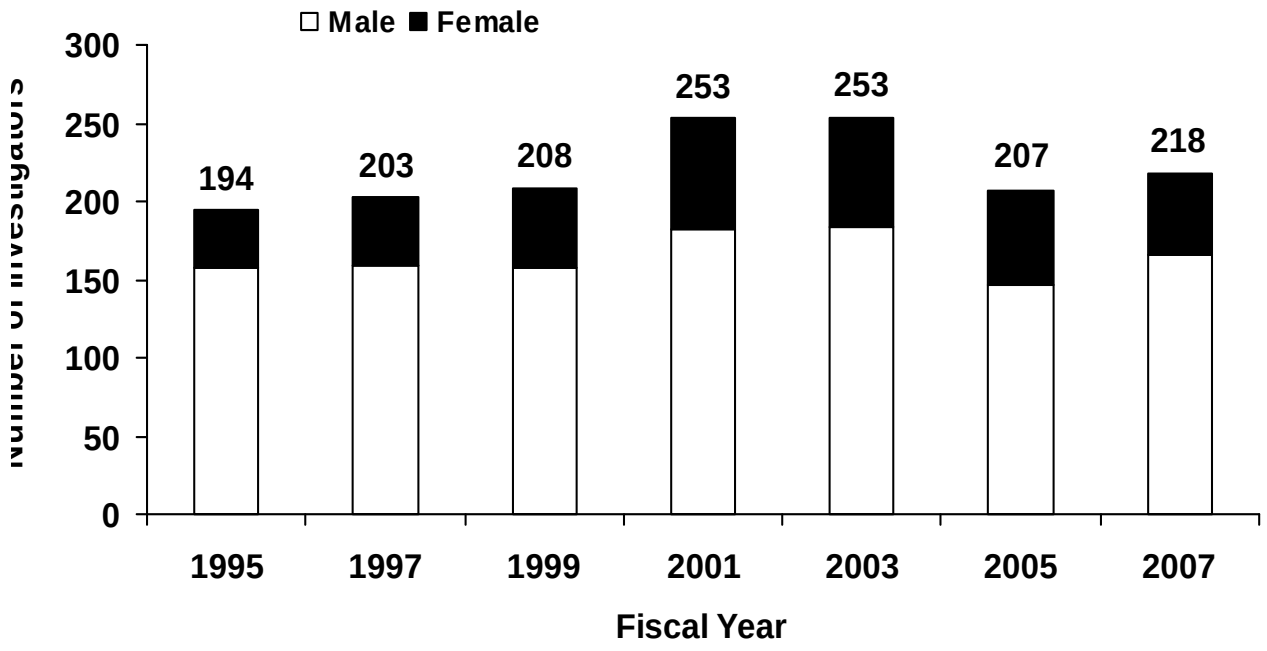


FIGURE 6: FIRST-TIME R01 APPLICANTS AND SUCCESS RATES BY GENDER, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007

The number of first-time R01 applications (n = 308) is 40 percent for females and 60 percent for males, which is identical to their success rates, 40 percent and 60 percent, respectively (n = 47).

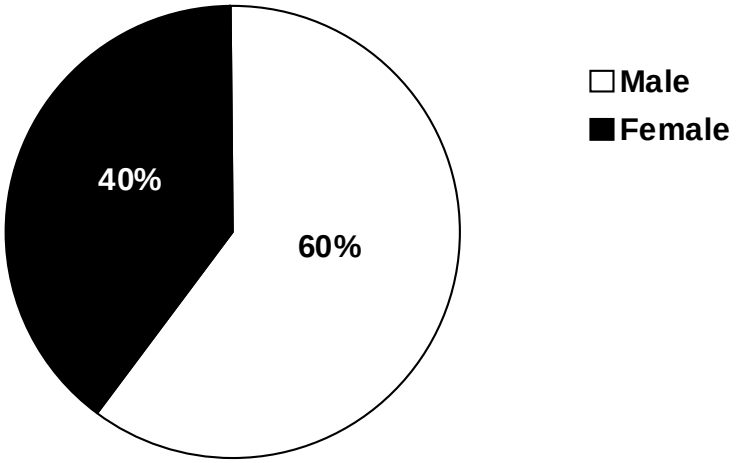
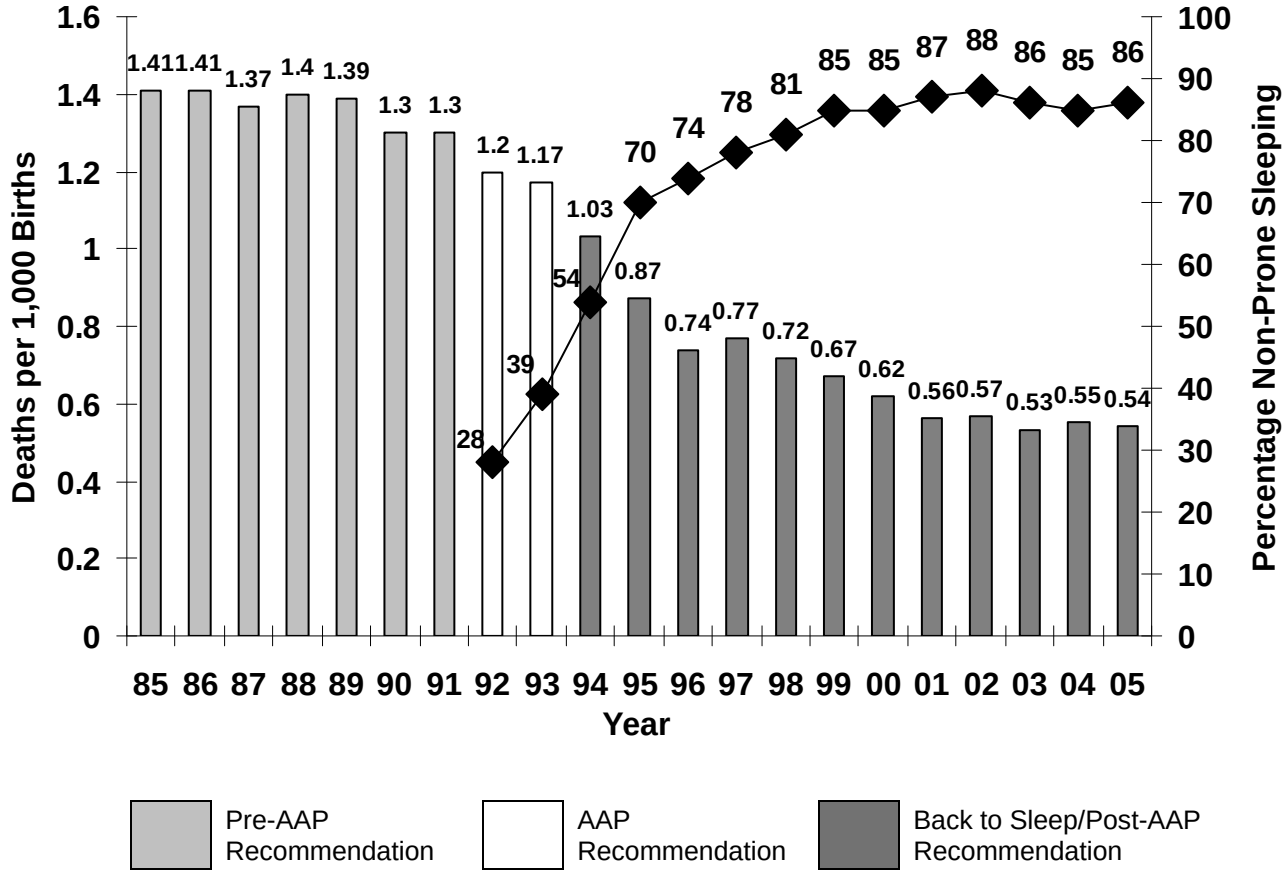


FIGURE 7: SUDDEN INFANT DEATH SYNDROME (SIDS) RATES AND SLEEP POSITION



Sleep Position Source: NICHD Household Survey; SIDS Rate Source: National Center for Health Statistics, Centers for Disease Control and Prevention

FIGURE 8: PAPERS PUBLISHED FOR THE NEONATAL RESEARCH NETWORK (NRN), FISCAL YEAR 1990 THROUGH FISCAL YEAR 2008

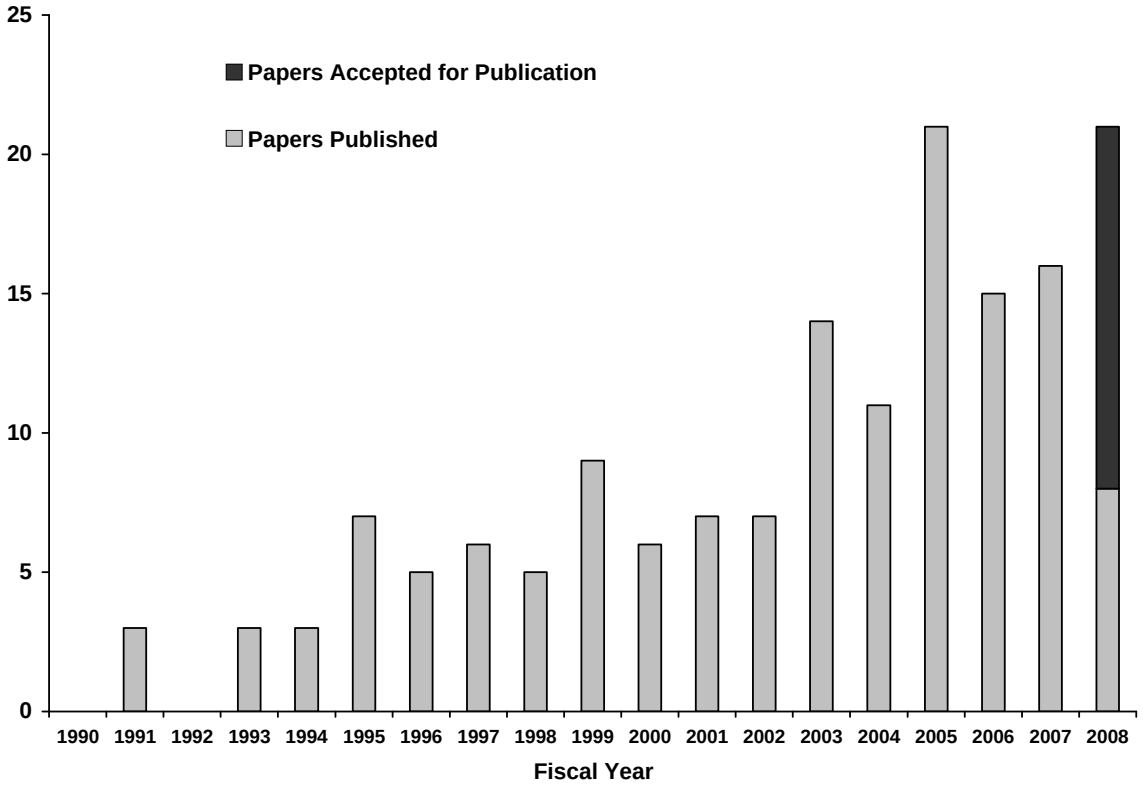


FIGURE 9: TIMELINE OF RECRUITMENT AND FOLLOWUP FOR NEONATAL RESEARCH NETWORK (NRN) STUDIES

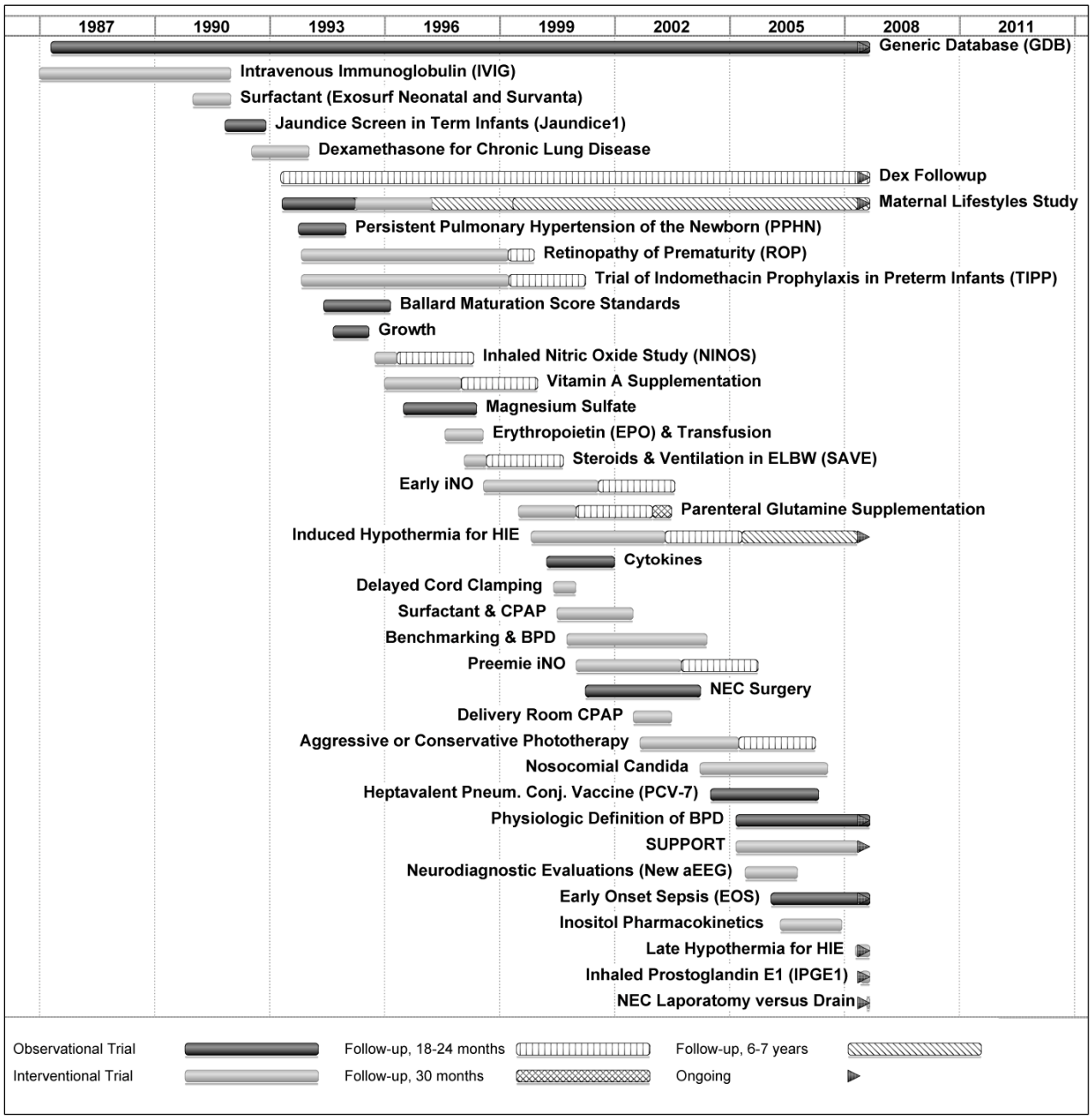


FIGURE 10: PAPERS PUBLISHED FOR THE MATERNAL-FETAL MEDICINE UNITS (MFMU) NETWORK, 1993 THROUGH 2008

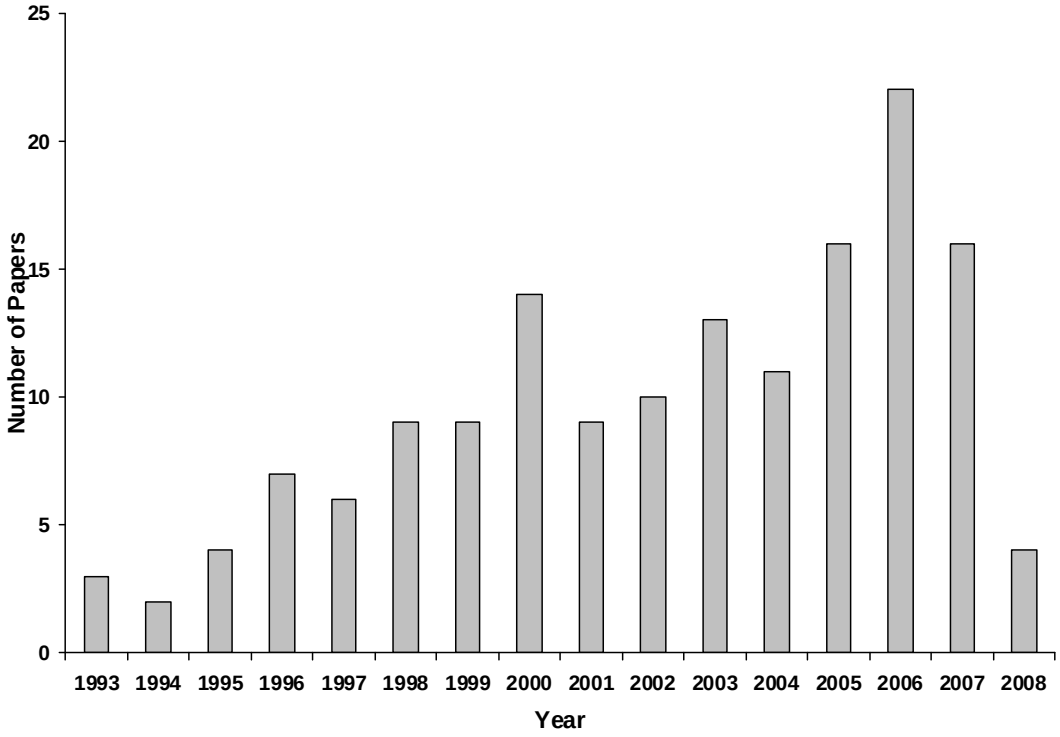


FIGURE 11: TIMELINE FOR RECRUITMENT AND FOLLOWUP OF MATERNAL-FETAL MEDICINE UNITS (MFMU) NETWORK STUDIES

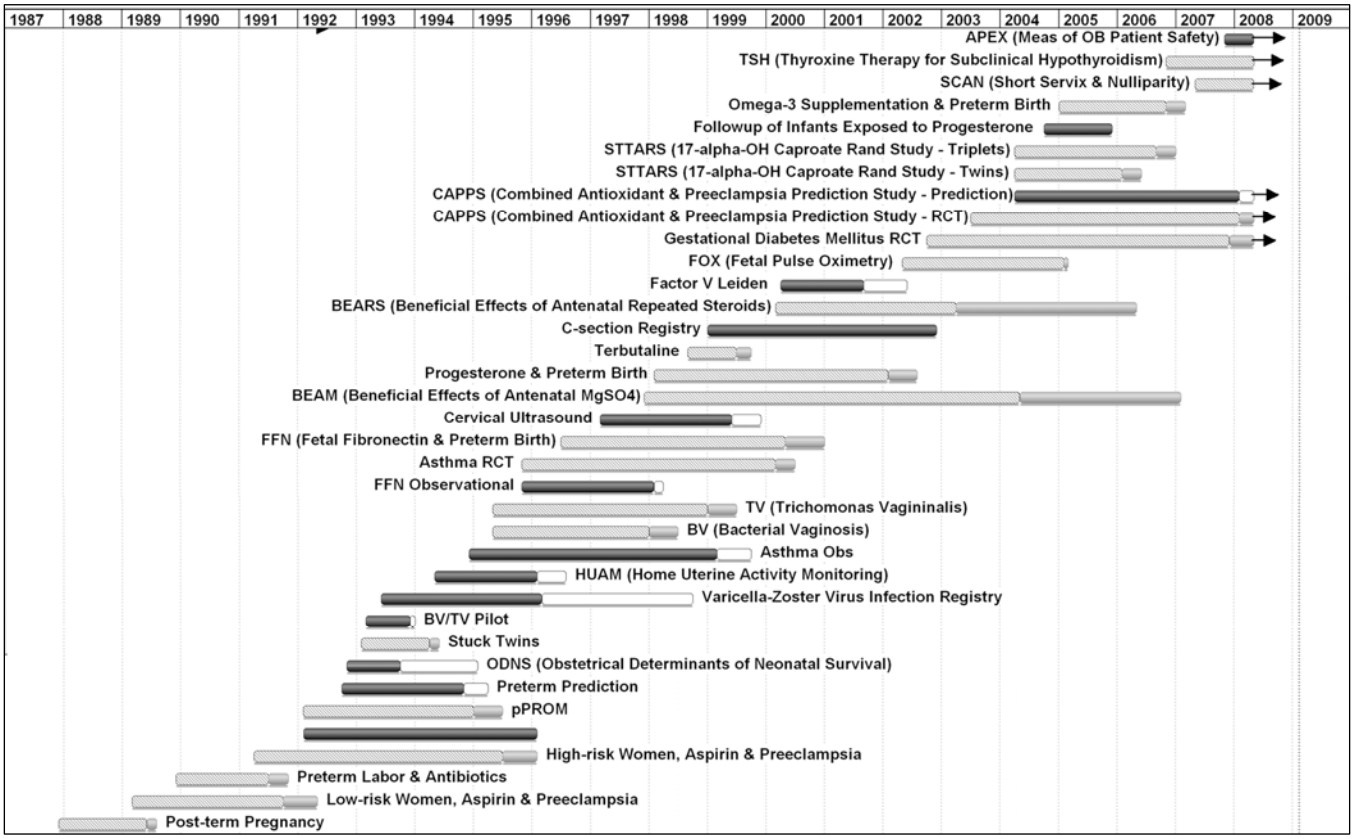


TABLE 2: MATERNAL-FETAL MEDICINE UNITS (MFMU) NETWORK TRIALS, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2008

Study Purpose/Description	Type of Study/ Intervention	Primary Outcome/ Sample Size	Status
FOX: Fetal Pulse OXimetry Trial			
Randomized controlled trial (RCT) to determine if fetal pulse oximetry affects overall cesarean delivery rate, cesarean delivery rate for fetal distress	Two-arm Trial	Cesarean Delivery/ 10,000 Participants	Enrollment complete; manuscript published in *New England Journal of Medicine*
Progesterone Follow-up Study			
Determine whether there is a difference in achievement of developmental milestones and/or physical health between children exposed to progesterone and controls	Observational Cohort Study	Ages and Stages Questionnaire; Developmental Milestones/ 348 Participants	Enrollment complete (n = 278); manuscript published in *Obstetrics & Gynecology*.
STTARS (17-α-OH caproate in Twins and Triplets: A Randomized Study)			
Double-masked placebo-controlled trial of whether 17-α hydroxyprogesterone prevents preterm birth in multi-fetal pregnancies	Weekly 17-OHPC (1 ml IM with 250mg) or Placebo	Preterm Delivery at Less than 35 Weeks of Gestation/ 600 Twin Pregnancies and 120 Triplet Pregnancies	Enrollment complete (n = 661 twins; n = 134 triplets); twin findings published in *New England Journal of Medicine*
RCTof Omega-3 Supplementation to Prevent Preterm Birth			
Double-masked placebo-controlled trial to determine whether Omega-3 in conjunction with 17-OHPC reduces the risk of preterm delivery in women at high risk for spontaneous preterm delivery	Weekly 17-OHPC (1 ml IM with 250mg) with Daily 2,000 mg Omega-3 or Placebo	Preterm Delivery at Less than 37 Weeks of Gestation/ 800 Participants	Enrollment complete (n = 852); plenary at Society for Maternal-Fetal Medicine 2008 meeting
BEAM Trial: Beneficial Effects of Antenatal Magnesium Sulfate in Prevention of Cerebral Palsy			
Double-masked, placebo-controlled trial to determine if antenatal Magnesium Sulfate can reduce the risk of cerebral palsy in offspring for women who deliver preterm at 24 to 31 weeks of gestation	$MgSO_4$ or Placebo	Composite outcome of death before 1 year of age or cerebral palsy at 24 months of age/ 2,220 Participants	Enrollment complete; No. 1 plenary at Society for Maternal-Fetal Medicine 2008 meeting
Gestational Diabetes Mellitus (GDM) Trial			
RCT with additional observational cohorts to test whether identification and dietary treatment of mild GDM reduces neonatal morbidity and mortality in women at 24 to 29 weeks of gestation, normal fasting blood sugar, abnormal three-hour glucose tolerance test	Treatment versus Standard Care	Fetal Composite/ 700 (Trial Participants); 1,050 (Cohorts)	Enrollment complete (n = 1,889); analysis underway

Study Purpose/Description	Type of Study/ Intervention	Primary Outcome/ Sample Size	Status
CAPPS (Combined Antioxidant & Preeclampsia Prediction Studies)			
Double-masked placebo-controlled trial to determine if antioxidants reduce serious maternal and infant complications associated with pregnancy-related hypertension in nulliparous women with a singleton gestation	Vitamin C and E or Placebo	Fetal Death at Less than 20 Weeks of Gestation or Composite/ 10,000 (RCT); 4,000 (Observational)	Enrollment: RCT = 9,844 (as of 1/11/08), Observational = 2,321 (as of 1/11/08)
TSH Trial: A Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy			
Double-masked placebo-controlled trial to determine whether thyroxine treatment for subclinical hypothyroidism or hypothyroxinemia diagnosed during the first half of pregnancy is associated with intellectual improvement in offspring	Thyroxine or Placebo	Intelligence Quotient (IQ) at Five Years of Age/ 1,000 (500 per Strata)	23,210 Screened; 441 Enrolled (as of 1/11/08)
SCAN (Short Cervix And Nulliparity)			
Double-masked placebo-controlled trial to determine whether 17-α hydroxyprogesterone prevents preterm birth in nulliparous women with short cervix	Weekly 17-OHPC (1 ml IM with 250mg) or Placebo	Preterm Delivery at less than 37 Weeks of Gestation/ 500 Women	10 Randomized (as of 07/31/07)
APEX (Measurement of Obstetrical Patient Safety)			
Develop a set of valid quality measures for obstetric care; evaluate specific measures, processes, & outcomes	Observational Study		Protocol, data forms being finalized; pilot conducted November to December 2007; full study started April 2008

APPENDIX A: BIOSKETCHES OF BRANCH PERSONNEL

Stephanie Wilson Archer, M.A., joined the PPB in April 2007 as the program coordinator for the Neonatal Research Network (NRN). Ms. Archer has a master's degree in sociology from George Mason University with interests in social networks and social and developmental neuroscience. She brings more than 12 years' experience in project management/international development and more than seven years' experience in academic/research libraries to the PPB.

Rosemary D. Higgins, M.D., is a board-certified neonatologist who joined the Branch in January 2003. She is the program scientist for the NICHD NRN and Maternal Lifestyles Study. Prior to joining the Branch, she held faculty positions at New York University Medical Center and at Georgetown University. Dr. Higgins is a member of the Society for Pediatric Research and American Pediatric Society, is the NICHD liaison to the Vermont Oxford Network Database Advisory Committee, and is a fellow of the American Academy of Pediatrics (AAP). She is also the neonatology editor for the *American Journal of Perinatology*. Dr. Higgins' area of expertise is retinopathy of prematurity.

John V. Ilekis, Ph.D., joined the Branch in June 1999. He holds a Ph.D. in biology with specialization in molecular biology. Prior to joining the PPB, Dr. Ilekis was a research assistant professor in the Department of Obstetrics and Gynecology at the University of Illinois, Chicago. His main scientific responsibilities include managing basic research grants on the physiology, biochemistry, and molecular biology of the placenta, uterus, and cervix. He has particular research interests in the basic mechanisms underlying the diseases of spontaneous preterm birth and preeclampsia. Dr. Ilekis is also a program scientist for the Genomics and Proteomics Network for Preterm Birth Research (GPN/PBR).

Susan Pagliaro joined the Branch in November 2001. She has more than 15 years' experience in the areas of maternal-fetal medicine and adolescent health. Ms. Pagliaro earned her bachelor's degree in public health with a focus on community health education from the University of Massachusetts. Her organizational skills and interest in clinical trials led her to the NIH, where she serves as a clinical trials specialist and the coordinator of both the Maternal-Fetal Medicine Units (MFMU) Network and the Maternal-Fetal Surgery Network. In 2006, Ms. Pagliaro received an NIH Merit Award for "Superior commitment, dedication, and accomplishment in achieving the designation of Best Practices for the NICHD's MFMU Network."

Tonse Raju M.D., D.C.H., F.A.A.P., is a board-certified neonatologist who joined the PPB in June 2002. He is the program scientist/medical officer for the PPB portfolios of neonatal research grants, training grants, and Small Business Innovative Research/Small Business Technology Transfer programs; he is also the project officer for the Cochrane Neonatal Review Group contract. Dr. Raju is the NICHD liaison for the Vermont Oxford Network Neonatal Encephalopathy Registry, Cochrane Collaboration Child Health Advisory Board; the AAP Committee on Fetus and Newborn, the Executive Committee of the AAP Section on Perinatal Pediatrics. He is a fellow of the AAP and holds membership in the American Pediatric Society, the Society for Pediatric Research, and the American Osler Society. He has served as the associate editor for the *Journal of Investigative Medicine*, and *AAP NeoReviews*.

Uma M. Reddy, M.D., M.P.H., joined the Branch in September 2003. Board certified in obstetrics and gynecology and maternal-fetal medicine, she was a Robert Wood Johnson Clinical Scholar and received her master's in public health from Johns Hopkins University. Dr. Reddy completed her obstetrics and gynecology residency at the Johns Hopkins Hospital and her maternal-fetal medicine fellowship at Thomas Jefferson University Hospital. Dr. Reddy manages translational and clinical research grants in obstetrics and maternal-fetal medicine and serves as a program scientist for the Stillbirth Collaborative Research Network (SCRN) and the GPN/PBR. Dr. Reddy is a fellow of the American College of Obstetricians and Gynecologists (ACOG), a member of the Society for Maternal-Fetal Medicine, and a maternal-fetal medicine specialist at National Naval Medical Center.

Caroline Signore, M.D., M.P.H., is a board-certified obstetrician/gynecologist who joined the Branch in October 2006. Dr. Signore is one of the Branch's program officers managing the obstetric portfolio and is a program scientist for the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network. She completed her obstetrics and gynecology residency at the University of Florida and received her master's in public health from George Washington University. She came to the Branch from the NICHD's Division of Epidemiology, Statistics, and Prevention Research. Dr. Signore is a fellow of ACOG and a member of the Society for Pediatric and Perinatal Epidemiology Research.

Catherine Spong, M.D., joined the Branch in January 2000 and is board certified in maternal-fetal medicine and obstetrics and gynecology. Dr. Spong is the program scientist for the MFMU Network and has been Branch chief since January 2001. She is an associate editor of *Obstetrics & Gynecology* and *William's Obstetrics*, while also serving as a maternal-fetal medicine specialist at INOVA Alexandria hospital. Dr. Spong is the NICHD liaison for the ACOG Committee on Obstetric Practice, the Society for Maternal-Fetal Medicine Executive Board, and the Liaison Committee of Obstetrician/Gynecologists. She is a fellow of ACOG and a member of the Society for Maternal-Fetal Medicine, the Society for Gynecologic Investigation, the Society for Neuroscience, and the Perinatal Research Society.

Marian Willinger, Ph.D., is the NICHD special assistant for SIDS, responsible for the direction of the Institute's SIDS research program, including the development of the Institute's third, five-year research plan *Targeting SIDS: A Strategic Plan*. She also serves as an expert on SIDS within the U.S. Public Health Service. Dr. Willinger is a program scientist for the Collaborative Home Infant Monitoring and Evaluation Study, the PASS Network, and the SCRN. She also recently completed contracts to support SIDS epidemiological studies. Dr. Willinger has been involved in the development, implementation, and evaluation of the *Back to Sleep* campaign and serves as a consultant to the AAP Task Force on Infant Positioning and SIDS. During the last five years, Dr. Willinger has participated in NIH- and government-wide activities, including the Advisory Board of the National Center on Sleep Disorders Research and the Interdisciplinary Research Workgroup of the NIH Roadmap.

APPENDIX B: PPB-SUPPORTED STUDIES THAT HAVE IMPACTED CLINICAL PRACTICE

Topic	Impact on Clinical Practice	NICHD Research Contributing to the Impact on Clinical Practice
Antenatal corticosteroid therapy for fetal maturation	ACOG Committee on Obstetric Practice. (2008). Antenatal corticosteroid therapy for fetal maturation (ACOG Committee Opinion No. 402). *Obstet Gynecol, Mar;111*(3), 805-807.	MFMU Network trials: • Wapner, et al. (2006). Single versus weekly courses of antenatal corticosteroids: Evaluation of safety and efficacy. *AJOG, Sep;195*(3), 633-642. • Wapner, et al. (2007). Long-term outcomes after repeat doses of antenatal corticosteroids. *NEJM, Sep20;357*(12), 1190-1198. NIH Consensus Development Conferences: • Antenatal corticosteroids revisited: Repeat courses. (2000). NIH Consens Statement. Aug 17-18; 17(2), 1-10. • The effect of antenatal steroids for fetal maturation on perinatal outcomes. (1994). NIH Consens Statement. Feb 28-Mar 2;12(2), 1-24.
Breast milk and extremely low birth weight infants: neurodevelopmental outcome improvement	Promotion of breastfeeding	NRN studies: • Vohr, et al. (2007). Persistent beneficial effects of breast milk ingested in the NICU on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics, Oct;120*(4), e953-e959. • Vohr, et al. (2006). Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics, Jul;118*(1), e115-e123.
Cesarean delivery on maternal request	ACOG Committee on Obstetric Practice. (2007). Cesarean delivery on maternal request (ACOG Committee Opinion No. 394). *Obstet Gyncol, Dec;110*(6), 1501.	• National Institutes of Health State-of-the-Science Conference Statement: Cesarean delivery on maternal request. *Obstet Gynecol. 2006;107*, 1386-1397. • MFMU Network study on VBAC; Silver, et al. (2006). Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol, Jun;107*(6), 1226-1232.
Induction of labor for vaginal birth after cesarean (VBAC) delivery	ACOG Committee on Obstetric Practice. (2006). Induction of labor for vaginal birth after cesarean delivery (ACOG Committee Opinion No. 342). *Obstet Gyncol, Aug;108*(2), 465-468.	• MFMU Network study; Landon, et al. (2004). Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. *NEJM, Dec 16;351*(25), 2581-2589. • R01-HD039441; Macones, et al. (2005). Maternal complications with vaginal birth after cesarean delivery: A multi-center study. *AJOG, Nov;193*(5), 1656-1662.
Infection and neurodevelopmental impairment	Increased vigilance for followup for extremely low birth weight infants	NRN study; Stoll, et al. (2004). Neurodevelopmental and growth impairment among extremely low birth-weight infants with neonatal infection. *JAMA, Nov 17;292*(19), 2357-2365.

Topic	Impact on Clinical Practice	NICHD Research Contributing to the Impact on Clinical Practice
Inhaled Nitric Oxide (NO)	Limitation of use of inhaled NO in preterm infants; followup shows no difference in outcomes.	NRN studies: • Van Meurs, et al. (2005). Inhaled nitric oxide for premature infants with severe respiratory failure. *N Engl J Med, Jul 7;353*(1), 13-22. • Hintz, et al. (2007). Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. *J Pediatr, Jul;151*(1), 16-22, 22, e1-e3.
Late-preterm infants	• Engle, Tomashek, Wallman, & **the** AAP Committee on the Fetus and Newborn. (2007). "Late preterm" infants: A population at Risk. *Pediatrics, Dec;120*(6), 1390-1401. • ACOG Committee on Obstetric Practice. (2008). Late preterm infants (ACOG Committee Opinion No. 404). *Obstet Gyncol, Apr;111*(4), 1029-1032.	NICHD Workshop on Late-Preterm Infant
Neonatal pain management and morphine therapy	Most centers have reduced or stopped using continuous intravenous (IV) morphine for very low birth weight infants. Even intermittent IV morphine use has declined, with increasing use of fentanyl.	Anand, et al. (2004). Effects of morphine analgesia in ventilated preterm neonates: Primary outcomes from the NEOPAIN randomised trial*. Lancet, 363*, 1673-1682.
Perinatal risks associated with assisted reproductive technology	ACOG Committee on Obstetric Practice. (2005). Perinatal risks associated with assisted reproductive technology (ACOG Committee Opinion No. 324). *Obstet Gyncol*, Nov;106(5 Pt 1), 1143-1146.	NRN study; Stevenson, et al. (1998). Very low birth weight outcomes of the NICHD Neonatal Research Network, January 1993 through December 1994. *AJOG*, *Dec;179*(6 Pt 1), 1632-1639.
Periviable calculator	Source of information for threatened preterm birth at 22 weeks' to 25 weeks' gestation	NRN study; Tyson, et al. (2008). Intensive care for extremely premature newborns: Moving beyond gestational age thresholds. *NEJM, 358*(16), 1672-1681.
Screening for fetal chromosomal abnormalities	ACOG Committee on Practice Bulletins. (2007). Screening for fetal chromosomal abnormalities (ACOG practice bulletin 77). *Obstet Gyncol*, *Jan;109*(1), 217-227.	• NICHD Workshop: Incorporating First-Trimester Down Syndrome Studies Into Prenatal Screening • Prenatal screening: Incorporating the first trimester screening. *Seminars in Perinatology, 2005;29*(4). • Reddy & Mennuti. (2006). Incorporating first-trimester Down syndrome studies into prenatal screening: Executive summary of the NICHD workshop. *Obstet Gyncol, 107*, 167-173.
Subclinical hypothyroidism in pregnancy	ACOG Committee on Patient Safety and Quality Improvement. (2007). Subclinical hypothyroidism in pregnancy (ACOG Committee Opinion No. 381). *Obstet Gyncol, Oct;110*(4), 959-960.	Casey, et al. (2007). Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstet Gynecol, May;109*(5), 1129-1135.

Topic	Impact on Clinical Practice	NICHD Research Contributing to the Impact on Clinical Practice
Sudden Infant Death Syndrome (SIDS)	AAP Medical Home Initiatives for Children with Special Needs Project Advisory Committee. (2004). Policy Statement: Organizational principles to guide and define the child health care system and/or improve the health of all children. *Pediatrics, 113*, 1545-1547. AAP Task force on SIDS. (2005). The Changing Concept of SIDS: Diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk. *Pediatrics, 116*, 1245-1255.	• National Infant Sleep Position (NISP) Study Public Access Web site: http://dccwww.bumc.bu.edu/ChimeNisp/Main_Nisp.asp • Hauck, et al. (2002). The contribution of prone sleeping position to the racial disparity in SIDS: The Chicago Infant Mortality Study. *Pediatrics, 110*, 772-780. • Li, et al. (2003). Infant sleep position and SIDS risk in California, 1997-2000. *Am J Epidemiol, 157*, 446-455. • Willinger, et al. (1998). Factors associated with the transition to nonprone sleep positions of infants in the United States: The NISP Study. *JAMA, 280*, 329. • Mitchell, et al. (1999). Changing infants' sleep position increases risk of SIDS. *Arch Pediatr Adoles Med, 153*, 1136-1141. • Hauck, et al. (2003). Sleep environment and the risk of SIDS in an urban population: The Chicago Infant Mortality Study. *Pediatrics, 111*, 1207-1214. • Kemp, et al. (1998). Softness and potential to cause rebreathing: Differences in bedding used by infants at high and low risk for SIDS. *J Pediatrics, 132*, 234-239. • Flick, et al. (2001). Sleep position and the use of soft bedding during bed sharing among African American infants at increased risk for SIDS. *J Pediatrics, 138*, 338-343. • Mosko, et al. (1997) Infant arousals during mother-infant bed sharing: implications for infant sleep and SIDS research. *Pediatrics, 100*, 841-849. • McKenna, et al. (1997). Bed sharing promotes breastfeeding. *Pediatrics, 100*, 214-219. • Unger, et al. (2003). Racial disparity and modifiable risk factors among infants dying suddenly and unexpectedly. *Pediatrics, 111*(2), E127. • Kemp, et al. (2000). Unsafe sleep practices among infants dying suddenly and unexpectedly: Results of a four year, population-based, death-scene investigation study of SIDS and related death. *Pediatrics, 106*(3). • Ramanathan, et al. (2001). Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. *JAMA, 285*, 2199-2207. • Vernacchio, et al. (2003). Sleep position of low birth weight infants. *Pediatrics, 111*, 633-640.

Topic	Impact on Clinical Practice	NICHD Research Contributing to the Impact on Clinical Practice
		• Willinger, et al. (2000). Factors associated with caregivers' choice of infant sleep position, 1994-1998: The NISP Study. *JAMA, 283*, 2135-2142.
Use of progesterone to reduce preterm birth	ACOG Committee on Obstetric Practice. (2003). Use of progesterone to reduce preterm birth (ACOG committee opinion 291). *Obstet Gyncol*, *Nov;102*(5 Pt 1), 1115-1116. (In revision for publication in 2008)	• MFMU Network trial; Meis, et al. (2003). Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *NEJM, 348*, 2379-2385. • MFMU Network study; Northen, et al. (2007). Followup of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. *Obstet Gynecol, Oct;110*(4), 865-872.
Whole-body cooling	Blackmon, Stark, & the AAP Committee on the Fetus and Newborn. (2006). Hypothermia: A neuroprotective therapy for neonatal hypoxic-ischemic encephalopathy. *Pediatrics*, *Mar;117*(3), 942-948.	NRN Network study; Shankaran, et al. (2005). Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *NEJM, Oct13;353*(15), 1574-1584.

APPENDIX C: PPB-SUPPORTED CONFERENCES AND WORKSHOPS, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007

American Academy of Pediatrics (AAP)-NICHD Workshop on Research in Neonatology was held on January 15-16, 2004, in collaboration with the Section on Perinatal Pediatrics of the AAP in Rockville, Maryland. The focus of the workshop was to: address the basic and translational research issues in neonatal-perinatal medicine; identify knowledge gaps; and review the role of promising methods, such as genomics, proteomics, imaging, and molecular biology, in neonatal-perinatal research fields. Other issues addressed included: training needs for physician-scientists in neonatal-perinatal medicine; board-certification issues; and strategies to overcome the dwindling pool of physician-scientists, especially of women and underrepresented minorities in academic medicine. For the agenda and a list of conference participants, visit http://www.nichd.nih.gov/about/meetings/2004/ppb_aapneonate.cfm.

Workshop of the Border of Viability, held March 4-5, 2004, addressed one of the most complex areas in perinatal-neonatal medicine—care of the mother who delivers an infant at the border of viability—referred to as "periviable" gestation in the resulting paper. Output from this conference includes the following: Higgins RD, Delivoria-Papadopoulos M, & Raju T. (2005). Executive summary on the workshop on viability. *Pediatrics, 115*, 1392-1396.

Fetal Treatment: Needs Assessment and Future Directions Workshop was held on August 16-17, 2004, in collaboration with the NIH Office of Rare Diseases (ORD) and the National Heart, Lung, and Blood Institute (NHLBI). The purpose of the workshop was to develop a plan for the surgical, maternal-fetal, and neonatal evaluation and treatment of pregnancies which might benefit from *in utero* therapy and assess the need and appropriate mechanisms for dissemination of innovations in maternal-fetal treatment. Participants included experts in maternal-fetal therapy, representatives from involved specialty societies and organizations, and others interested in the area. Experts presented specific topics emphasizing areas of controversy or knowledge gaps when applicable. Output from the meeting includes: Chescheir NC, & Socol M. (2005). The NIH Workshop on Fetal Treatment: Needs assessment and future directions. *Obstetrics & Gynecology, 106*(4), 828-833.

Incorporating First-Trimester Down Syndrome Studies into Prenatal Screening Workshop, held December 16-17, 2004, was a collaborative effort between the NICHD, the Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG), and the March of Dimes (MOD). The field of prenatal screening is rapidly developing, with the emergence of alternative testing approaches earlier in pregnancy making decisions about prenatal screening increasingly complex. The purpose of this workshop was to summarize available research on first trimester and second trimester screening for aneuploidy and the effect of incorporation of first trimester screening as part of prenatal screening. The workshop determined that sufficient evidence supported the incorporation of first-trimester testing into prenatal practice in the United States, and that providers should focus on the most effective implementation of various screening schema based on patient counseling and available resources. The output of this workshop includes the following:

- Reddy UM, & Mennuti MT. (2006). Incorporating first-trimester Down syndrome studies into prenatal screening: Executive summary of the NICHD Workshop. *Obstetrics & Gynecology, 107*(1), 167-173.
- Prenatal screening: Incorporating the first-trimester studies; proceedings of an NICHD Workshop, December 16-17, 2004. (2005). *Semin Perinatol, 29*(4), 189-279.

Improving Maternal Nutrition to Optimize Pregnancy Outcome: Development of a Research Plan, held November 8-9, 2004, in Bethesda, Maryland, was co-sponsored by the International Society for the Development of Origins of Health and Disease and the U.S. Agency for International Development. The goal was to develop a coherent research strategy for improving maternal and infant nutrition, focusing on periconception, and optimizing fetal development, antenatal factors and adaptation/transition. National and international experts met and identified research gaps and strategies addressing both basic and clinical research needs, as well as issues unique to the developing world that may impact on development and implementation of evidence-based programs. Specific topics included: factors operative in the periconceptual period, including adequacy of diet; determinants of optimal fetal development; mechanisms and reversibility; and adaptations and transition, including how the baby is managed after birth. An executive summary of the meeting is being prepared.

Hypothermia for Perinatal Asphyxia Workshop, co-sponsored by the NIH ORD, occurred on May 18-19, 2005. The goal of the meeting was to discuss the current state of knowledge about the benefits of hypothermia for perinatal asphyxia and to identify knowledge gaps. This information will help professional organizations to make evidence-based practice recommendations related to this critical topic. Output from this conference includes: Higgins RD, Raju TNK, Perlman J, Azzopardi DV, Blackmon LR, Clark RH, & Edwards, et al. (2006). Hypothermia and perinatal asphyxia: Executive summary of the NICHD Workshop. *J Pediatr, 148*, 170-175.

Care of Near-Term Fetus and the Near-Term Neonate Workshop, co-sponsored by the NIH ORD and the MOD, was held July 18-19, 2006. Obstetric and neonatal care at 35 weeks' to 37 ("near-term") weeks' gestation presents a unique set of challenges and dilemma. At these gestations, women are often assumed to be at low risk, and their newborn infants considered normal. Yet, near-term newborn infants need close monitoring, and some require intensive care. Such infants are at high risk for complications related to preterm birth, such as respiratory distress syndrome, transient tachypnea of the newborn, patent ductus arteriosus, hypothermia, apnea, infection, feeding difficulty, necrotizing enterocolitis, and hyperbilirubinemia. Compared to their term counterparts, re-hospitalization rates are more common in near-term infants due to higher incidence of apnea, meningitis, seizures, intracranial hemorrhage, and bilirubin-induced brain injury and Kernicterus. The purpose of the workshop was to invite a multidisciplinary team of experts to discuss management of these infants. The executive summary from the meeting was published in *Pediatrics* in October 2006, and manuscripts from presentations delivered at the conference were published in *Seminars in Perinatology* in 2006.

Oxygen in Neonatal Therapies: Controversies and Opportunities for Research, a meeting held August 8-9, 2006, examined the use of oxygen in newborn care. Evidence for its use has large gaps including appropriate oxygenation in normal infants, use of oxygen in newborn

resuscitation, and appropriate use of oxygen in preterm and extremely preterm infants. Short-term and long-term benefits and risks have been described; however, optimal use of oxygen in newborns is not well defined. The goals of this meeting were to review the current evidence for care practices and define gaps for which knowledge regarding care is lacking. It is hoped that information (or lack thereof) presented at this meeting will lead to new initiatives and advancement of knowledge and care in the field. The executive summary from this meeting, which was co-sponsored by the NIH ORD, was published as: Higgins RD, Bancalari E, Willinger M, & Raju TNK. (2007). Executive summary of the Workshop on Oxygen in Neonatal Therapies: Controversies and opportunities for research. *Pediatrics*, *119*(4), 790-796.

Infertility Treatment and Adverse Pregnancy Outcomes Workshop was held September 12-13, 2005, and was co-sponsored by the PPB and the Reproductive Sciences Branch at the NICHD, the NIH ORD, and the NIH Office of Research on Women's Health (ORWH). Increased use of assisted reproductive technology (ART) over the past two decades has allowed thousands of infertile couples to have children; ART births currently accounting for 1 out of 100 births in the United States. ART is a significant contributor to preterm delivery and associated risks of preterm birth through an increased rate of multiple gestations. However, recent evidence of higher rates of adverse pregnancy outcomes even in singleton pregnancies associated with ART, including increased preterm and term low birthweight, very low birthweight, preterm delivery, fetal growth restriction, genetic disorders, and congenital anomalies, is cause for concern. Children who are born as a result of intracytoplasmic sperm injection (ICSI) also have an increased risk of a major congenital malformation compared to those born as a result of spontaneous conception. The role of underlying infertility, the direct effects of the ART/ICSI treatments and other maternal-fetal exposures in producing the increased risk of adverse pregnancy outcomes remain poorly understood. The goals of this meeting were to review the current research in this area, identify gaps, stimulate research to better define the range of adverse fetal outcomes, and understand the mechanisms underlying adverse pregnancy outcomes associated with infertility treatments. The executive summary is available at: Reddy UM, Wapner RJ, Rebar R, & Tasca R. (2007). Infertility, assisted reproductive technology, and adverse pregnancy outcomes: Executive summary of an NICHD Workshop. *Obstet Gynecol, 109*, 967-977.

NIH State-of-the-Science Conference Cesarean Delivery on Maternal Request, held March 27-29, 2006, followed a planning process that began in January-February 2005 and was co-sponsored by the NIH Office of Medical Applications of Research, the National Institute of Diabetes and Digestive and Kidney Diseases, the ORWH, and the National Institute on Nursing Research. Despite the Healthy People 2010 goal of reducing cesarean section rates to 15 percent, rates have continued to increase, with a 25-percent increase since 1995 to the 2002 rate of 26.1 percent (National Center for Health Statistics/Centers for Disease Control and Prevention [CDC]). In part, this increase is due to elective cesarean deliveries (patient choice) and is compounded by hospitals refusing to allow vaginal births after cesarean (VBAC), given the rigorous requirements and potential liability. It is estimated that elective cesareans account for 4 percent to 18 percent of all cesarean deliveries. Thus, the acceptance of elective cesarean sections by the medical community will likely result in further dramatic increases in cesarean delivery rates. Elective cesareans may also have gained popularity due a link to fewer problems with pelvic floor disorders and flexibility for the medical community. However, this procedure

is being adopted without evaluation of the evidence, both of the potential benefits (urogynecologic) and risks (maternal and fetal). This conference allowed for a rigorous evaluation of the evidence and for raising public health awareness of the findings to design research goals and guide practitioners in discussing the options and assessing risks and benefits. Visit http://consensus.nih.gov/2006/2006CesareanSOS027main.htm for more information on the conference. Output from the conference included:

- NIH State-of-the-Science Conference Statement (Eds. C. Spong & U. Reddy). (2006). Cesarean section on maternal request. *Obstet Gynecol, 107*, 1386-1397.
- Cesarean delivery on maternal request: Manuscripts from the experts. (Oct;2006). *Seminars in Perinatology*.

Perinatal stroke is a poorly understood neurological entity affecting the fetus and the newborn that has potential for significant neurological morbidity. The **Perinatal Stroke Workshop**, held August 21-22, 2006, and co-sponsored by the National Institute of Neurological Disorder and Stroke (NINDS), the NIH ORD, and United Cerebral Palsy, invited a team of experts from multidisciplinary fields to discuss the current state of knowledge, identify knowledge gaps, and develop and prioritize a research agenda related to perinatal stroke. Because the topic is of interest to specialists from diverse fields, invitations to participate in the meeting were extended to specialists from fetal and perinatal medicine, hematology, general pediatrics, neonatology, pediatric neurology, neuropathology, neuro-radiology, hematology, genetics, pediatric/perinatal pathology, and epidemiology. Output from this meeting includes: Raju TN, Nelson KB, Ferriero D, Lynch JK, & the NICHD-NINDS Perinatal Stroke Workshop Participants. (2007). Ischemic perinatal stroke: Summary of a workshop sponsored by the NICHD and the NINDS. *Pediatrics, 120*, 609-616.

The **Prenatal Imaging: Sonography and MRI Workshop**, held September 18-19, 2006, was co-sponsored by the NIH ORD, National Institute on Biomedical Imaging and Bioengineering, the Department of Defense, the Telemedicine & Advanced Technology Research Center of the U.S. Army Medical Research and Material Command, and the Gottesfeld-Hoeler-Carlson Foundation. Since its introduction in 1983, magnetic resonance imaging (MRI) has revolutionized imaging. Dramatic reduction in image acquisition time has allowed introduction of this technology for fetal evaluation and currently, high-quality fetal images are routinely achievable without the need for fetal sedation. As currently used, MRI has been compared to sonography in some settings, or as an adjunct for further evaluation of an anomaly detected by sonography. Fetal MRI improves diagnostic accuracy for major central nervous system anomalies, mid-brain anomalies, cortical destruction and hemorrhage. In addition, MRI is suggested to improve diagnostic accuracy for posterior cleft palate, neck and thoracic anomalies, urinary tract anomalies in the setting of oligohydramnios, and fetal spinal cord anomalies. The role of prenatal MRI remains undefined and the potential for MRI to evaluate fetal metabolic functions (e.g., brain, placenta, other) is looming on the horizon and may revolutionize fetal diagnosis and evaluation. The goals of this workshop were to identify the research knowledge and gaps for fetal MRI and ultrasound and to define a research agenda for this area. Output from this meeting includes: Reddy UM, Filly RA, & Copel JA. (2008). Executive summary—Prenatal imaging: Ultrasonography and MRI. *Obstet Gynecol, 112*, 145-157.

Preeclampsia is one of the most common complications of pregnancy and remains a major cause of fetal and maternal morbidity and mortality. **Preeclampsia: A Pressing Problem**, a meeting held September 22-23, 2006, with support from the PPB and the NIH ORD, the NIH Office of Disease Supplements, and the MOD, sought to address several promising areas of research on this topic, including the inappropriate remodeling of uterine vasculature, increased oxidative stress level, immune response to paternal antigens, production of autoantibodies, and abnormal placental production of endothelial growth factors and their antagonists. The purpose of this workshop was to bring together lead researchers in the field to discuss their particular area of research, identify scientific gaps, and stimulate collaborative research. Output from this meeting includes: Ilekis JV, Reddy UM, & Roberts JM. (2007). Preeclampsia—a pressing problem: An Executive Summary of an NICHD Workshop. *Reprod Sci, 14*, 508-523.

The PPB hosted the **Antenatal Testing: A Reevaluation** meeting on August 27-28, 2007, with support from the NIH ORD, ACOG, and AAP. Fetal death occurs in 6.4 out of 1,000 pregnancies in the United States, although experts believe this figure is an underestimate. In half of these deaths, antepartum risk factors are present and, of those with risk factors, 25 percent to 75 percent may be amenable to prenatal modification. In addition, cerebral palsy affects 2 out of 1,000 live born infants, while neonatal encephalopathy occurs in 1.9 to 3.8 out of 1,000 births and may result in permanent neurologic disability, similar to cerebral palsy. In the vast majority of cases, the neurologic insults resulting in neonatal encephalopathy seem to arise in the antepartum period, before the onset of labor. Multiple techniques for antepartum assessment of fetal well-being have been developed in attempts to identify at-risk fetuses and enable prevention of adverse outcomes, such as stillbirth and central nervous system injury resulting in neonatal encephalopathy and/or cerebral palsy. However, the evidence base supporting the use of these techniques and the recommendation of one modality over another is limited. It is not clear which antenatal testing strategy best reduces perinatal mortality and morbidity. The goals of this meeting were to review the current evidence for antepartum assessments and define gaps for which knowledge regarding care is lacking. By identifying and highlighting research needs, participants aimed to stimulate research to fill those gaps and advance knowledge and care in the field. Output from this meeting includes an issue of *Seminars in Perinatology* devoted to manuscripts based on the workshop presentations (Signore C, Spong CY, guest editors. [2008]. Antenatal testing: A reevaluation. *Semin Perinatol, 32,* 231-332). An executive summary is currently in progress.

The **Stillbirth Definition and Classification System: Developing an International Consensus for Research**, held October 22-24, 2007, sought to address issues related to stillbirth. According to official international reports, approximately 3.3 million stillbirths occur each year. Such deaths in less developed countries, which account for 97 percent of reported stillbirths, are not always registered and, therefore, the true burden is likely underestimated. As more research into the causes of stillbirth is being conducted internationally, including the PPB-led Stillbirth Collaborative Research Network, an internationally agreed upon classification system is urgently required for the comparison of results of these various research studies and to devise prevention strategies for stillbirth. The workshop, co-sponsored by the SMFM, First Candle, and the NIH ORD, gathered international experts and researchers to address the definition of stillbirth, define goals of a stillbirth classification system, and the identify necessary criteria for assigning cause

of death. International researchers presented their research studies and evidence for various classification systems. An executive summary is currently in progress.

Preconception Care Research: Improving Birth Outcomes and Reproductive Health, held April 14-15, 2008, in Bethesda, Maryland, was co-sponsored by a number of agencies and organizations, including: NIH ORD, ORWH, CDC, MOD, SMFM, and ACOG. Preconception care is important to women's health across the reproductive lifespan and is a proven strategy to improve reproductive outcomes. It is increasingly clear that factors, such as nutrition, exercise and drug use, can influence the quality of male and female gametes, perhaps many years prior to conception. Investigators now believe that peri- and post-conception insults to eggs, embryos, and fetuses can lead to childhood, adolescent, and adult health disorders and diseases. The goal of preconception care is to promote healthy families and facilitate optimal prenatal, intrapartum, and postpartum maternal and fetal health. Because many events before and around the time of fertility may affect pregnancy outcomes, such care focuses on women's health long before pregnancy begins. This workshop brought together a broad spectrum of experts, including clinicians and basic science and translational investigators, to define a multidisciplinary framework for developing an agenda in preconception care research by addressing the current state of knowledge, identifying emerging issues or continuing gaps in knowledge, and exploring future opportunities for research. Output from the meeting will be a research agenda on preconception care.

Electronic Fetal Heart Rate Monitoring: A Re-evaluation, held April 27-28, 2008, was co-sponsored by ACOG and the SMFM. From May 1995 to November 1996, the NICHD held a succession of workshops to develop standardized and unambiguous definitions for fetal heart rate tracings; the series culminated in recommendations for interpreting fetal heart rate patterns (*AJOG*, 1997*;177*, 1385-1390). The definitions from the workshops allowed the predictive value of monitoring to be assessed more meaningfully and allowed more evidence-based clinical management of intrapartum fetal compromise. In the ensuing decade, these definitions have been utilized and taught throughout the country, and new interpretations and definitions have been proposed, including three-tier and five-tier systems. The Society of Obstetricians and Gynaecologists of Canada *Consensus Guidelines for Fetal Health Surveillance* presents the three-tiers (e.g., normal, atypical, and abnormal) versus the two-tiered (e.g., reassuring/nonreassuring) classification; other research (Parer, *AJOG*, 2007;*197*, 26.e1-26.e6) presents a five-tiered management grading system based on Homeland Security Risk categories. The objective of this workshop was to convene experts in the field to clarify the terminology used in electronic fetal heart rate monitoring, based on the ACOG Practice Committee Bulletin (December 2005), the executive summary from the NICHD workshop (*AJOG*, 1997;*177*: 1385-1390), and subsequent expert articles. Participants reviewed the evidence and provided a current source document for the practicing clinician on the terminology to be used in electronic fetal monitoring.

Surgeon General's Conference on the Prevention of Preterm Birth, held June 16-17, 2008, was co-sponsored by the Office of the Surgeon General, the NICHD's Division of Epidemiology, Statistics, and Prevention Research, the PPB, the ORWH, the NIH Office of Women's Health, the MOD, AAP, ACOG, and the Association of Women's Health, Obstetric, and Neonatal Nurses. The purpose of the conference, which was outlined in the Prematurity

Research Expansion and Education for Mothers who Deliver Infants Early (PREEMIE) Act (P.L. 109-450), included the following tasks:

- Increase awareness of preterm birth as a serious, common and costly public health problem;
- Review the findings and reports issued by the Interagency Coordinating Council on Low Birth Weight and Preterm Birth (a group convened in response to recommendations of the Secretary's Advisory Committee on Infant Mortality and headed by the Health Resources and Services Administration and the NICHD at the behest of the DHHS Secretary), key stakeholders, and other relevant entities; and
- Establish an agenda for activities in both the public and private sectors that will speed the identification of and treatments for the causes of and risk factors for preterm labor and delivery.

More information about the conference, including the final presentations to the Surgeon General, is available at http://www.nichd.nih.gov/about/meetings/2008/SG_pretermbirth.cfm.

The PPB is working with the NIH Office of Medical Applications of Research and other partners to convene **Consensus Development Conference: Vaginal Birth after Cesarean (VBAC)**, which is anticipated in 2009. Despite the Healthy People 2010 goal of decreasing cesarean births, the cesarean delivery rate in the United States has been steadily rising since 1996, reaching an all-time high (more than 30 percent) in 2005. A major driving force behind the increase in cesarean births is the declining rate of VBAC. In 1996, delivery by VBAC peaked at 28.3 percent; by 2004, VBAC rates had dropped to 9.2 percent. The coupling of this trend with a concomitant increase in the primary cesarean rate portends a continued escalation in the overall national cesarean delivery rate. Numerous studies have examined the outcomes of repeat cesarean delivery and VBAC, which is associated with risks of uterine rupture, need for hysterectomy or transfusion, and endometritis. Repeat cesarean, especially multiple repeat cesarean deliveries, also carries risk of hemorrhage and hysterectomy due to placental implantation problems, as well as maternal infectious morbidity and neonatal respiratory morbidity. The goal of this conference is to raise awareness of this complicated issue, allow for a rigorous evaluation of existing evidence, and develop a statement that advances understanding of VBAC that will be useful to health professionals and the public. Such a consensus statement will be of immediate use to practitioners and pregnant patients as they discuss risks and benefits associated with planned mode of delivery. An organizational meeting of NICHD, OMAR, other institutes, and federal partners was held in October 2007. Dr. F. Gary Cunningham accepted the committee's invitation to chair the future consensus panel. The next stage in preparation, a planning committee meeting of federal partners and other experts and organizational representatives (e.g., ACOG, AAP, SMFM, American College of Nurse Midwives), was held in August 2008.

Other PPB-sponsored meetings include the following:

- Long-Term Followup of Prenatal Drug Exposure: Challenges and Opportunities; co-sponsored by the National Institute on Drug Abuse; March 2004 http://www.drugabuse.gov/NIDA_notes/NNvol19N3/Conference.html
- Obesity meeting; June 12-13, 2006

- Necrotizing Enterocolitis (NEC) meeting; July 10-11, 2006; output from the conference includes: Grave GD, Nelson SA, Walker WA, Moss RL, Dvorak B, Hamilton FA, Higgins R, & Raju TN. (2007). New therapies and preventive approaches for NEC: Report of a research planning workshop. *Pediatr Res, Oct;62*(4), 510-514.
- Neonatal Hyperbilirubinemia in Egypt: Shedding Light on Improving Outcomes (Cairo, Egypt); March 12, 2007; co-sponsored by the National Research Center Egypt and Fogarty International Center; output from this conference includes: *Severe Neonatal Hyperbilirubinemia and Bilirubin-induced Brain Damage in Egypt, White Paper for Action Plan Based on the Workshop*, submitted to the NACHHD Council in May 2007, and to the Egyptian Ministry of Health in June 2007 (through U.S. Department of Health and Human Services).
- Improving the Treatment of Neonatal Seizures; sponsored by NINDS; May 31-June 1, 2007

APPENDIX D: BRANCH SOLICITATIONS, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007

REQUESTS FOR APPLICATIONS (RFAS)

- HD-02-103: Maternal Lifestyle Study Phase IV
- HD-02-104: *The Collaborative Home Infant Monitoring Study (CHIME)*
- HD-02-105: *Data Coordinating Center for the Cooperative Multi-center Maternal-Fetal Medicine Units (MFMU) Network*
- HD-02-106: *Data Center for the Cooperative Neonatal Research Network (NRN)*
- HD-03-004: *Prenatal Alcohol Exposure among High-Risk Populations: Relationship to SIDS*
- HD-03-018: *Research into Mechanisms of Fetal Growth Restriction*
- HD-03-104: *Mentored Specialized Clinical Investigator Development Awards in the NRN*
- HD-03-106: *NIH-DC Initiative to Reduce Infant Mortality in Minority Populations*
- HD-03-112: *Data Coordinating Center for the NIH-DC Initiative to Reduce Infant Mortality in Minority Populations*
- HD-04-002: *Genomic and Proteomic Network for Premature Birth Research (GPN/PBR)*
- HD-04-010: *NICHD Cooperative Multi-center NRN*
- HD-04-023: *NICHD MFMU Network*
- HD-05-108: *PHASE II of the Community Child Health Network (CCHN)*
- HD-05-111: *Prenatal Alcohol in SIDS and Stillbirth Network*
- HD-06-001: *Data Coordination and Analyses Center for the CCHN*
- HD-06-104: *MSCIDA for the MFMU Network and the NRN*
- HD-07-002: *Data Coordinating Center for the NICHD Cooperative Multi-center NRN*
- HD-07-004: *Data Coordinating Center for the NICHD Cooperative Multi-center MFMU Network*
- HD-07-102: *Limited Competition: Study of Attitudes and Factors Affecting Infant Care*

PROGRAM ANNOUNCEMENTS (PAS)

- PA-02-102: *The Role of Gene-Environmental Interactions Underlying the Health Disparity of Premature Birth* (sponsored by the NICHD, National Institute on Environmental Health Sciences, and the National Institute on Nursing Research)
- PA-03-135: *Women's Mental Health in Pregnancy and the Postpartum Period* (sponsored by the National Institute of Mental Health, the National Institute on Drug Abuse, and the NICHD)
- PA-04-027: *Reducing Preterm and Low Birth Weight in Minority Families*
- PA-080103: *Adverse Outcomes of Assisted Reproductive Technologies (P01)*

- PA-080104: Adverse Outcomes of Assisted Reproductive Technologies (R01)

APPENDIX E: PUBLICATIONS FROM PPB STAFF AND PPB-SUPPORTED NETWORKS, 2004 THROUGH 2008

(PPB staff names appear in **bold**. * Denotes staff peer-reviewed publications)

SELECTED PPB PORTFOLIO PUBLICATIONS

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APPENDIX F: PPB STAFF AWARDS, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2008

- Plain Language Award, NIH, 2004, Willinger
- Director's Award, NIH, 2004, Spong
- Society of Maternal Fetal Medicine Research Award, 2004, Spong
- NIH Award of Merit, 2005, Ilekis
- Director's Award, NIH, 2005, Willinger
- Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry, Honor Award for Silo Busters: Collaborative Success, 2005, Spong
- Donald Eitzman Lecturer, University of Florida, 2005, Raju
- NIH Award of Merit, 2005, Reddy
- NIH Award of Merit, 2005, Higgins
- NIH Award of Merit, 2005, Raju
- Most Distinguished Physician Award, American Association of Physicians of Indian Origin, 2006, Raju
- NIH Award of Merit, 2006, Willinger
- NIH Award of Merit, 2006, Raju
- NIH Award of Merit, 2006, Reddy
- NIH Award of Merit, 2006, Higgins
- NIH Award of Merit, 2006, Pagliaro
- Best Practices Network from the NIH Roadmap: Initiative Inventory and Evaluation of Clinical Research Networks, 2006, MFMU Network Award, Pagliaro
- Thomas Cone Jr. Lecturer, AAP National Convention, 2007, Raju
- Society for Maternal Fetal Medicine Achievement Award, 2008, Spong

APPENDIX G: EXPERT PANEL MEMBERS

Michele Walsh, M.D.
Medical Director, Neonatal Intensive Care Unit (NICU)
Rainbow Babies & Children's Hospital, Case Medical Center
Professor, Department of Pediatrics, Case Western Reserve University
Cleveland, Ohio

Yoel Sadovsky, M.D.
Scientific Director
Magee-Women's Research Institute
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Mark Phillippe, M.D.*
Professor & Chairman
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Burlington, Vermont

George R. Saade, M.D.
University of Texas Medical Branch
Department of Obstetrics & Gynecology
Galveston, Texas

Sherin Devaskar, M.D.*
Professor
Department of Pediatrics
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, California

Michael Myers
Columbia University
Co-Principal Investigator
New York, New York

Hal Lawrence, M.D.
Vice President, Practice Activities
American College of Obstetricians and Gynecologists
Washington, D.C.

Alan Fleishman, M.D.
Senior Vice President and Medical Director
March of Dimes
White Plains, New York

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