

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Eunice Kennedy Shriver National Institute
of Child Health and Human Development

Prematurity Research at the NIH

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PREMATURITY RESEARCH AT THE NIH

Executive Summary

Preterm birth, and its consequences, remains one of the most intransigent research problems in the area of pregnancy and delivery. To date, few successful interventions have been identified. However, a wide array of research projects is being funded by a number of institutes and centers at the National Institutes of Health (NIH), lead by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Some progress has been made in identifying the factors that may be connected with prematurity, as well as ruling out certain treatments that have not been shown to be effective. In addition to continuing strong support for this research, the Surgeon General has asked the NICHD to take the lead on planning the upcoming Surgeon General's conference on prematurity, scheduled for late spring of 2008.

Introduction

In its report on the Fiscal Year 2007 budget for the Department of Health and Human Services, the House Committee on Appropriations stated:

“The Committee commends NICHD for its commitment to reducing the incidence of premature birth and its consequences through its longstanding support for the Maternal-Fetal Medicine Unit and the Neonatal Research Network, as well as the new Genomics and Proteomics Network for Premature Birth Research. The Committee is pleased that NICHD is one of the sponsors of an Institute of Medicine study to define and address the health related and economic consequences of premature birth and looks forward to publication of the recommendations. The Committee encourages NICHD to expand its research on the causes of preterm labor and delivery and improving the care and treatment of preterm and low birth weight infants, to work with the Office of the NIH Director to develop a strategic plan for research, and to coordinate its research with other institutes.” (House report No. 109-515, page 104/105)

In response to this request, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) prepared the following report.

Background

Preterm delivery is a major public health problem. The preterm birth rate is over 12 percent of all live births, accounting for over half a million premature births each year. One in eight infants in the United States is born preterm. Preterm birth is the leading cause of death among African-American infants and the second leading cause in Caucasians, and is associated with an increased risk for developmental disabilities. Over the last two decades, preterm birth rates have risen approximately 30%, reaching 12.7% in 2005. Concomitant with the rise in preterm births is a rise in multi-fetal gestations, due in a large part to the increased use of assisted reproductive technologies. Between 1980 and 2000 there was a 74% increase in twin births in the US. Not only were there more twin births, but a higher proportion of the twins were delivered preterm, with 22% more twin births delivering preterm in 1996-1997 than in 1981-1982.

The sequelae of preterm birth include immediate complications, specifically mortality, and significant morbidity. In 2001, preterm birth surpassed birth defects as the leading cause of neonatal mortality. Preterm birth accounts for one of five children with mental retardation, one of three children with vision impairment and almost half of children with cerebral palsy. In the long term, children born low birth weight have an increased risk for cardiovascular disease such as myocardial infarction, stroke and hypertension as an adult, an increased risk for diabetes as an adult, and a possible increase in cancer risk. For the mother, delivering preterm increases her risk of a subsequent preterm delivery.

One of the strongest risk factors for preterm birth is having had a prior preterm birth; after a prior preterm birth, the incidence of a recurrent preterm birth in a subsequent pregnancy is increased two-fold from the background risk. In addition, there is a racial disparity in both

the baseline rates and recurrence rates of preterm births. In 2004, preterm births occurred in 11.5% of Caucasian women and 17.9% of non-Hispanic black women. With one previous preterm birth, the recurrence rates of preterm births are 15-20% in Caucasian women, and 26% in black women. The recurrence risk varies depending on the gestational age of the prior preterm birth. In addition, the gestational age of subsequent preterm delivery is similar to the initial preterm birth, with 50% delivering within one week and 70% delivering within two weeks of the previous preterm delivery. Increasing numbers of prior preterm deliveries also increases the risk of subsequent preterm delivery, and those with a recent preterm birth are at higher risk of recurrence than those with a remote preterm birth followed by a term delivery. The additive risk associated with multiple prior preterm births is especially evident when early preterm births are considered. Women with one prior preterm delivery <35 weeks have a 16% recurrence risk, those with 2 early preterm deliveries have a 41% risk, and those with 3 prior preterm deliveries have a 67% risk of subsequent preterm birth before 35 weeks.

Of the overall 500,000 preterm births each year, 75 percent are late preterm births (34-36 weeks gestation), accounting for around 40 percent of Neonatal Intensive Care Unit (NICU) admissions. Not only has the preterm birth rate increased in the U.S. from 9.1% (1981) to 12.7% (2005) but the rate of late preterm deliveries has also increased from 7.3% (1992) to 9.1% of all live births in 2005. There is a paucity of information on indications for delivery at 34-36 weeks and relationship to neonatal and infant outcomes. In 2005, 292,627 singleton deliveries were between 34-36 weeks and a sizable proportion (22.4%) had no apparent indication for delivery (no medical, obstetric, major congenital anomalies, or labor noted on the birth certificate). Of note, slightly early deliveries without specific indications had significantly higher neonatal and infant mortality rates compared to deliveries due to isolated spontaneous labor. These infants are at higher risk for sepsis, pneumonia, hypoglycemia, temperature instability, hyperbilirubinemia, and potential kernicterus, feeding difficulties, white matter damage, seizures, apnea, and remain at risk for higher rates of re-hospitalization after initial hospital discharge. Compared to their term counterparts, late preterm infants appear to be at a higher risk for Sudden Infant Death Syndrome (SIDS) and higher neurological and developmental morbidities rates during childhood. This group of infants has not been well studied and may account for a portion of the increase in neurodevelopmental disorders.

Women for whom the current pregnancy will lead to their first delivery (nulliparas) comprise about 40% of pregnant women in the United States. A recent national registry study showed that the rate of preterm delivery among low risk primiparas increased 50% in the past decade. Because there is no information from previous pregnancy outcomes to guide assignment of risk or mitigating interventions, adverse pregnancy outcomes in nulliparas are especially unpredictable. At least 12% of nulliparous women will have a preterm delivery, with associated higher rate of neonatal mortality and long term morbidity.

In December 2006, the Prematurity Research Expansion and Education for Mothers who Deliver Infants Early Act was signed into law (P.L.109-450). Among other things, the new law authorizes an Interagency Coordinating Council on Prematurity and Low Birthweight, which is being implemented at the department level, directs the U.S. Surgeon General to

convene a meeting on preterm birth. The NIH will participate in the council. This meeting is scheduled to occur in late spring of 2008.

NIH Institute and Center Research Activities

The NIH is committed to understand the causes of preterm birth and reduce the incidence of preterm birth and its consequences. Although the NICHD supports the bulk of research in this area, NIH funded \$351M in FY 2007 and expects to spend approximately \$356M in subsequent years.

Eunice Kennedy Shriver NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

The mission of the NICHD is to ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve their full potential for healthy and productive lives, free from disease or disability, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation.

Research on preterm birth includes understanding the mechanisms, prediction and prevention of preterm delivery, the optimal management of preterm labor, optimal management of the preterm neonate and the long-term implications of preterm delivery on both the infant and mother/family. The NICHD supports this work through the funding of investigator initiated applications, specific solicitations for individual grants as well as networks, the identification of high priority topics, and the identification and highlighting of gaps through the use of conferences and workshops. In addition to funding a wide range of extramural research, NICHD's intramural program includes a branch largely devoted to issues related to pregnancy, preterm birth and congenital anomalies.

One of the most successful approaches for testing research questions related to prematurity is NICHD's research networks, which allow researchers from across the country to coordinate their work and share data. Currently, three networks are being supported that deal with different aspects of the problem of prematurity and its consequences. The first, the Maternal Fetal Medicine Units (MFMU) Network (<http://www.bsc.gwu.edu/mfm>) conducts clinical studies to improve maternal, fetal and neonatal health emphasizing randomized-controlled trials. The aims of the Network are to reduce maternal, fetal and infant morbidity related to preterm birth, fetal growth abnormalities and maternal complications and to provide the rationale for evidence-based, cost-effective, obstetric practice. The MFMU Network is composed of 14 sites across the US and a data center. The Neonatal Research Network, also established in 1986, aims to improve the care and outcome of neonates, especially very low birthweight infants. Since its inception, several advances have been made to improve the survival of infants, and additional work is addressing complications in the areas of infection, breathing problems, and neurodevelopmental outcomes. Currently the NRN is composed of 16 clinical centers and one data center.

The newest network is the Genomic and Proteomic Network for Preterm Birth Research (GPN/PBR). An individual woman's risk of preterm birth may be determined by multiple factors including her genetic makeup and the way(s) that her genes control the expression of substances such as proteins, hormones, infection-fighting agents and other active agents that may affect her pregnancy. To search the myriads of human genes and proteins for abnormalities that could help explain preterm birth, the NICHD's Genomic and Proteomic Network for Preterm Research (GPN/PBR) was introduced as a five-year initiative in 2006. The main objective of this research network is to use wide-scale, high-output genomic and proteomic strategies to accelerate knowledge in the mechanisms responsible for premature birth. Approaches such as genome-wide scans and global serum protein profiling will be used to identify new biomarkers that increase the risk or are predictive of a preterm delivery and to delineate molecular mechanisms responsible for a preterm birth.

Understanding the mechanism

Approximately 50% of preterm births occur spontaneously following the premature onset of labor, 40% are medically-induced deliveries due to medical conditions endangering the mother and/or fetus, and 10 % of preterm births are associated with the premature rupture of fetal membranes leading to either a spontaneously or medically-induced delivery. Consequently, the cause(s) for a preterm delivery is dependent on its categorical type.

Research supported by the NICHD's Pregnancy and Perinatology Branch has indicated that spontaneous preterm birth has a number of possible causes. These include intrauterine infection/inflammation, uterine bleeding, excessive uterine stretch, maternal psychosocial stress, and fetal physiological stress. Certain causes are more prominent during certain stages of pregnancy. For example, intrauterine infection is associated more often with an early (less than 34 weeks) than a late spontaneous preterm delivery. (34-36 weeks). The physiological processes underlying these causes are currently an intense area of study.

The main pregnancy complications leading to a medically-induced preterm delivery are preeclampsia, fetal distress, and fetal growth restriction. Notably, preeclampsia is a major focus of research supported by NICHD since it is the primary reason for a medically-indicated, preterm delivery, accounting for approximately 40% of all medically induced preterm births. Preeclampsia is a pregnancy-specific, hypertensive disorder and occurs in about 4 % of all live-birth pregnancies. Researchers supported by the NICHD have shown that this disease is associated with a defect in the placenta which results in reduced blood flow between the mother and the fetus.

In addition, NICHD-funded researchers are exploring the use of drugs that can manipulate certain protective enzymes that can improve placental function. One enzyme being studied is a potent antioxidant defense protein called heme oxygenase-1 (HO-1), which has emerged in recent years as an important mediator of tissue protective and anti-inflammatory actions. It has been shown that HO-1 is crucial for keeping the human uterus in a relaxed state during pregnancy. A reduced level of placental HO-1 seems to be associated with a higher risk for preeclampsia. Thus, the unique combination of tissue protective and smooth muscle relaxing properties of the enzyme HO-1 make it an interesting target for treatment of preeclampsia.

Research has indicated that preterm premature rupture of the fetal membranes (pPROM) has multiple causes. They include chronic inflammation and /or infection, repeated stretching, maternal stress and trauma. The likelihood of pPROM being the cause for a preterm delivery is higher for an early than a late preterm delivery; approximately 21% and 8%, respectively. The most common causes for pPROM, currently under investigation, appear to be chronic inflammation and/or infection.

Prediction of Preterm Birth

Although progress is being made in understanding the possible causes and pathways involved in a preterm delivery, albeit not as rapidly as one would desire, the present challenge is to gain a much deeper understanding at the molecular level to aid in formulating effective interventions to prevent preterm birth.

Labor and fetal growth involves a complex interplay of factors and signaling molecules within the maternal, placental, and fetal tissues. Recent advances have implicated placental corticotropin-releasing hormone (CRH) as one of the primary endocrine mediators of spontaneous labor and possibly fetal development. No study has examined the prospective relationship between maternal CRH and fetal growth restriction. NICHD funded researchers have made substantial progress in this prospective study of women with a singleton pregnancy demonstrating that a single measurement of CRH at 33 weeks of pregnancy predicts fetal birth weight and identifies patients at high risk for preterm labor. These results, although not final, demonstrate that in humans, placental CRH directly participates in the physiologic processes of parturition and fetal growth and maturation, as evidenced by the prospective relationship between elevated CRH levels and increased risk for preterm birth and fetal growth restriction.

Cervical length seems to be a predictor of spontaneous preterm birth. However, the relationship between shortened cervical lengths present early rather than later (less than 26 and 26-34 weeks' gestation respectively) for predicting spontaneous preterm birth has not been determined. The NICHD's MFMU Network conducted a blinded, multicenter observational study of 183 women with a prior preterm birth. The trial showed that in high-risk women in the mid-trimester, shortened cervical length predicts early, but not later, spontaneous preterm birth. The results of this and other related studies of women at high-risk for preterm birth do point to an association between cervical length and diminished cervical competence. Additional research to assess preventive measures is needed.

Home Uterine Activity Monitors (HUAM) have been widely prescribed for patients in the anticipation that detecting those patients who were having frequent uterine contractions would identify those patients who would deliver preterm. However, a team of researchers supported by the NICHD's MFMU Network found that portable monitors that detect contractions of the uterus do not appear to be useful for identifying women likely to deliver preterm. This work has demonstrated the failure of this new technology to attain a more precise diagnosis, and has stopped its ineffective and expensive use from spreading.

Prevention of Preterm Birth

Despite studies of bed rest, tocolytic therapy (slowing or stopping uterine contractions), antibiotic therapy, and other strategies for prevention, no effective and reproducible method of preventing preterm delivery has been demonstrated. The strongest risk factor for the prediction of preterm delivery is having a prior preterm delivery. One of the few preventive measures for preterm birth to have shown promise in randomized trials is the use of progesterone agents, but the number of subjects reported in these trials is relatively small, and the populations treated and the methods of the trials differ.

A team of researchers supported by the NICHD's MFMU Network studied women who had a previous preterm delivery and therefore were considered at high risk for recurrent preterm delivery. This randomized double masked clinical trial compared weekly treatment by injection of 17 Alpha-hydroxyprogesterone caproate (17P) with placebo in women at high risk for preterm birth. Women receiving these injections starting at 16 to 20 weeks gestation had a significantly reduced risk of preterm delivery when compared to women receiving placebo injections. Infants of women treated with 17P had significantly lower rates of severe complications of prematurity. 17P is the first successful treatment demonstrated to reduce the risk of recurrent preterm delivery and improve neonatal outcomes in a subset of high-risk women. Further studies are required to determine if this treatment can be used for other populations of pregnant women at high risk for preterm delivery and if there are other progestational agents that may be equally effective and easier to administer.

The literature strongly supports a relationship between bacterial infection and preterm birth. However, studies involving randomized trials of antibiotics to reduce preterm birth have yielded mixed results. Fetal fibronectin (FFN) is a membrane protein which when detected in cervical or vaginal secretions of asymptomatic women has been associated with a more than 50-fold increased risk in preterm delivery. The use of antibiotics in women with a positive FFN was evaluated in another study supported by the NICHD's MFMU Network, and found that the use of a prolonged course of broad-spectrum antibiotics did not decrease the risk of spontaneous delivery and did not result in improved neonatal outcomes.

Caring for Preterm Newborns

Of the 12% of prematurely born infants in the US each year, more than 5% fail to grow appropriately in the womb due to placental insufficiency. Slow fetal growth, or fetal growth restriction (FGR), increases the risk of mortality and long-term neurological morbidity, including difficulties in infants' early learning. More than 70% of severe FGR infants develop learning disabilities and require special educational services. NICHD is supporting research that will test the effectiveness of an intervention in the NICU for such infants. In the project, care is being individualized to the infant's thresholds of sensitivity to sensory organs, expecting to show brain-based effects of the intervention for FGR infants, mediated by stress reduction.

Extremely low birth weight (ELBW) infants are at increased risk for developmental and behavioral abnormalities. While the beneficial effects of breast milk on cognition have been described, the effects of breast milk on neurodevelopment have not previously been evaluated. The NICHD Neonatal Research Network, in a large study of very small infants in

15 sites, collected detailed information on milk intake of extremely low birth weight infants as part of a large trial of glutamine supplementation. Infants given breast milk had an increase in several developmental scores, making efforts to enhance breast feeding and provision of breast milk to ELBW infants a high priority.

Nutrition and prevention of infection remain significant problems for this group of ELBW babies. Glutamine is one of the most abundant amino acids in breast milk and in blood, but is not included in standard solutions for intravenous nutrition. Glutamine showed significant promise in small human studies in adults for preventing infection and reducing death. Due to this finding, some intensive care nurseries had begun to supplement high-risk babies with glutamine. However, in the same Neonatal Research Network study, glutamine supplementation did not affect the rate of infection or the rate of death in the infants, providing sound information that glutamine supplementation for tiny babies should not be recommended at this time.

Stress or pain during the newborn period has been shown to cause permanent alterations in subsequent behavioral and/or physiological reactivity and to other stressors in later life in animal models. However, the cumulative effects of pain related to acute procedures in the immediate neonatal period, especially in the setting of the NICU, has received limited attention. NICHD-funded researchers examined the relationships between prior neonatal pain exposure (number of skin breaking procedures), and subsequent stress and pain response in preterm infants in the NICU. The study found that among the infants born at less than 28 weeks, the higher the cumulative pain experience, the lower the later physiological and behavioral response to stress and acute pain (“blunting response”). The differential effects of early pain on development of behavioral, physiologic and hormonal systems also indicate that immature infants are at greater risk for sustaining long-term damage from cumulative pain exposures. These findings underscore a continued need for future studies to develop methods to preventing pain, and to treat procedural pain with safe analgesics.

Future Directions

NICHD has been appointed as the lead federal agency in planning the upcoming Surgeon General’s Conference on the Prevention of Prematurity, June 2008. All of the NIH Institutes and Centers that are pursuing research related to prematurity will participate in the conference, along with other federal agencies, nonprofit organizations, and public members. At the close of the meeting, they will make recommendations to the Surgeon General regarding future directions for research (see Planning for Research, below).

In the strategic planning of the NICHD’s Pregnancy and Perinatology Branch, Premature Labor and Birth was highlighted as a critical area and one that needed novel approaches for the future including more focus on the etiology of preterm birth taking into consideration its multi-factorial nature, including utero-placental insufficiency, fetal growth abnormalities, and fetal stress. [*Pregnancy and Perinatology Branch (PPB) Strategic Plan, Fiscal Year 2005 through Fiscal Year 2010*] In the near term, NICHD is supporting a clinical trial on the proper clinical management of pregnant women with a shortened cervix (which has been shown to significantly increase the risk of preterm delivery); at this time, there is no

consensus or scientific evidence on the best approach. Another study just getting underway will test the effectiveness of simple, inexpensive approaches to reducing noise levels for ELBW babies being cared for in NICUs; excessive noise has been shown to pose risk factors for breathing and heart irregularities, sleep disturbances and poor growth. NICHD also plans to explore issues such as evaluating brain injury in premature infants with infections to develop interventions to improve their outcomes, and other clinical issues, such as whether the use of nitric oxide is beneficial to premature babies at any stage. The Institute also plans to hold several scientific meetings/workshops on issues such as the effects of assisted reproductive technology on adverse fetal outcomes, and conduct further work on the striking health disparity of preterm birth among African American women.

NATIONAL HEART, LUNG AND BLOOD INSTITUTE (NHLBI)

The NHLBI supports basic and clinical studies on the causes, therapy, and follow-up of conditions related to low birthweight and infant prematurity.

Bronchopulmonary dysplasia (BPD) is under study in an epidemiological investigation to document the neonatal and early childhood course and outcomes of all very low birthweight births in Wisconsin occurring during the calendar years 2003-2004. The study also will evaluate the proposed inflammatory hypothesis of the causes of BPD. In another project, cerebral injury is under study in a prematurely born baboon model of BPD.

Sheep models are being used to study persistent pulmonary hypertension of the newborn. The research focuses on the developmental regulation of oxygen-sensing in the lung, and nitric oxide-endothelin interactions that mediate changes in pulmonary vascular resistance of the developing lung.

Low birthweight is a risk factor for the development of human essential hypertension. One study of hypertension in a rat model focuses on the renal renin-angiotensin system and the cortical collecting duct, which are critical regulators of sodium balance. A second study tests the hypothesis that hypertension in low birthweight babies is initiated and sustained by abnormalities in the renin-angiotensin system and the nervous system.

In addition, the NHLBI is collaborating with NICHD to support the cooperative multi-center Neonatal Research Network, investigating treatment and management strategies to care for newborn infants, particularly low birthweight infants.

THE NATIONAL HUMAN GENOME RESEARCH INSTITUTE (NHGRI)

Two intramural laboratories at NHGRI focus on early stages of fetal development and elucidation of developmental disorders. One, which focuses on the formation of the central nervous system, investigates birth defects that affect normal embryonic development; the discovery of several genes associated with holoprosencephaly (failure of the embryonic brain to divide properly into left and right hemispheres) may shed light on fetal demise and developmental disabilities. Another lab uses genomic tools to study how an embryo develops into a functioning organism. The bulk of the research is on neural crest cells, a

group of stem cells that differentiate into a wide variety of tissues throughout the body. When the genetic machinery that controls neural crest development goes awry, it can cause many human diseases, some of which can affect a fetus or newborn.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

The NIEHS mission is to prevent disease and improve health by using environmental sciences to understand human biology and human disease. Environmental agents likely play a role in a number of early-stage diseases. NIEHS conducts research to investigate the role of environmental exposures during pregnancy to identify important triggers related to human development and to determine the importance of the timing of exposure on disease risk.

Much of the NIEHS portfolio related to the prenatal period is research aimed at better understanding how environmental exposures affect development and health including how disease outcomes such as cancer and asthma may originate. One NIEHS-funded study is exploring the relationship between living in the proximity of Superfund sites and adverse pregnancy outcomes, including prematurity. In addition, an NIEHS intramural study is pursuing basic questions on pregnancy and maternal and infant health such as preeclampsia and premature birth.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)

Preterm birth carries an increased risk for neurodevelopmental disabilities, including cerebral palsy, the leading cause of chronic neurological disability in survivors of premature birth. The NINDS supports research on the consequences of preterm birth for the developing brain and on the development of treatments and preventative strategies. Circulatory disturbances and oxygen deprivation are often associated with developmental damage to the preterm brain, and NINDS-supported research includes studies on how reduced oxygen and blood supply to the infant brain leads to damage or disrupted development, on genetic and other factors contributing to increased risk of brain hemorrhage in preterm infants, and on the long-term effects of neonatal administration of indomethacin, a drug shown previously by NINDS-supported research to lower the incidence of intraventricular hemorrhage.

The NINDS also sponsors studies using advance brain imaging techniques in preterm infants to identify damage and abnormalities predictive of later disability, trials of possible treatments to improve prognosis such as magnesium sulphate or thyroid hormone, as well as a multi-center clinical study to identify biomarkers and antecedents of damage to the white matter, which contains the brain's major neuronal connections.

NATIONAL INSTITUTE OF NURSING RESEARCH (NINR)

The NINR supports research on preterm birth and premature infants consistent with its mission to establish the scientific basis of care for individuals across the lifespan, regardless of disease or condition. NINR supports research into the causes and prevention of preterm birth, as well as the study of innovative methods to improve health and behavioral outcomes for preterm infants and their families. Recent projects conducted by NINR scientists have

examined: the effects of behavioral interventions for mothers of very low birthweight preterm infants on infant health outcomes and maternal well-being; techniques for promoting the transition of tube-fed preterm infants to oral feeding; the effects of a preterm infant exercise program on body mass development and bone strength; and health outcomes in adolescents who had been born preterm.

In one recent NINR-supported study, investigators tested an educational program, called Creating Opportunities for Parental Empowerment (COPE), among parents of premature infants. These parents often suffer high levels of stress, anxiety, and depression. In a randomized controlled clinical trial, parents who participated in the COPE program reported better understanding of the behaviors to expect from their infants, and they displayed more positive parent-infant interactions, compared to controls. Mothers had lower anxiety, depression, and overall parenting stress, and fathers were more involved in the infants' care. Infants of COPE parents averaged 3.8 fewer days in a newborn intensive care unit than control infants, which translated to a savings of approximately \$5,000 per infant. Given that about 500,000 infants are born in the U.S. annually, the COPE intervention potentially could save an estimated \$2.5 billion in U.S. health care costs each year.

Planning for Research on Prematurity

As mentioned above, NICHD's Pregnancy and Perinatology Branch conducted an intensive strategic planning process, resulting in a published plan for the years 2005-2010. Preterm birth was the lead topic identified as needing further study. The plan included recommendations that future investigations into the etiology of preterm birth should take into consideration the multifactorial nature of the problem, such as utero-placental insufficiency, fetal growth abnormalities, and fetal stress. Concerning prevention of preterm delivery, treatments geared toward the early changes, rather than contractions, should be pursued, and it was emphasized that studies need to include a diverse population. To achieve these ends, the plan strongly recommended using the networks of centers in place, including the tissue and data banks.

NICHD is not the only locus of research in the area of prematurity. NICHD, along with the Office of Research on Women's Health at the within the NIH Office of the Director, other federal agencies, and many outside organizations, participated in and contributed to a major Institute of Medicine (IOM) report, *Preterm Birth: Causes, Consequences and Prevention*, released July 2006. An extensive literature search was conducted, identifying in the process areas where there is little scientifically based evidence for approaches to preventing or treating the consequences of preterm birth. The report calls for improved data to better define the problem of preterm birth, including obtaining a better understanding of the economic outcomes for infants who are born preterm, and makes numerous recommendations for further research, including several that echo NICHD's strategic plan:

- Improving the methods of identifying and treating women at risk for preterm labor;
- Reviewing infertility treatments with the aim of reducing the number of multiple gestations;
- Studying multiple risk factors to facilitate the complex interactions associated with preterm birth;

- Expanding research into the causes and methods of prevention of racial-ethnic and socioeconomic disparities in the rates of preterm birth.

The IOM report will undoubtedly become a baseline of information in future planning efforts the upcoming, congressionally mandated, Surgeon General's meeting on prematurity, which will occur in the spring of 2008. Since the IOM report comprehensively covered the available evidence and information on research and prematurity, this meeting will be able to focus on prioritizing the greatest needs in research, including the need for translational and clinical research to more quickly make preventive measures, interventions and treatments available, and on whether professional or public education is needed to more effectively communicate information about this issue.

The report from the Surgeon General's meeting will identify and provide a timeline for a range of the most critical research and education priorities for addressing preterm birth.

Conclusion

Prematurity remains the major challenge facing researchers who work in the field of reproductive health and pregnancy, with broad ramifications. While extensive research is currently underway, few successful interventions have been identified. Future research efforts will focus on identifying the causative factors for preterm birth, and its prevention.