Testimony before the

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Committee on Energy and Commerce
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Prematurity and Infant Mortality: What Happens When Babies Are Born Too Early?

Statement of
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On behalf of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health, I appreciate the opportunity to provide the Committee with information about our research program on preterm birth and related issues. I am Dr. Catherine Spong, Chief of the Pregnancy and Perinatology Branch at the 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. As such, research on prematurity and its health outcomes falls squarely within the institute's mission.

Background

Preterm delivery is a major public health problem. The preterm birth rate in the U.S. is over 12 percent of all live births, accounting for over half a million premature births each year (1). Over the last two decades, preterm birth rates have risen approximately 30 percent. Concomitant with the rise in preterm births is a rise in multiple gestations, due in a large part to the increased use of assisted reproductive technologies. The number of twin births doubled between 1980 and 2006. (1).

In 2001, preterm birth is the leading cause of death in newborns who die within the first month. (2). It is the leading cause of death among African-American infants and the second leading cause of all infant mortality. In those who survive, 8 percent of all preterm births also have a major birth defect, and 16 percent of very preterm births (less than 32 weeks gestation) have a major birth defect: 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 adulthood, children born at a low birth weight have an increased risk for cardiovascular disease such as myocardial infarction, stroke and hypertension, and an increased risk for diabetes, and a possible increase in cancer risk (3). For the mother, delivering preterm increases her risk by nearly two-fold for a subsequent preterm delivery (4). In addition, there is a racial disparity in both the baseline and recurrence rates of preterm births. In 2004, preterm births occurred in 11.5 percent of Caucasian women and 17.9 percent of non-Hispanic black women. With one previous preterm birth, the recurrence rates of preterm births are 15-20 percent in Caucasian women, and 26 percent in black women. The additive risk associated with multiple prior preterm births is especially evident when early preterm births are considered. Women with one prior preterm delivery less than 35 weeks have a 16 percent recurrence risk, those with two early preterm deliveries have a 41 percent risk, and those with three prior preterm deliveries have a 67 percent risk of subsequent preterm birth before 35 weeks (5).

Of the over 540,000 preterm births in the United States each year, 70 percent are late preterm births (delivering between 34-36 weeks of gestation)(1). These infants account for about 40 percent of Neonatal Intensive Care Unit (NICU) admissions. Not only has the preterm birth rate increased in the U.S. from 9.1 percent (1981) to 12.3 percent (2008), but the rate of late preterm deliveries has also increased from 7.3 percent (1990) to 8.8 percent of all live births (2008). Data from 2008 indicate a slight decrease in the overall preterm birth rate, which primarily

reflects a decrease in late preterm births to 8.77 percent (1). These infants are at higher risk for sepsis, pneumonia, hypoglycemia, temperature instability, hyperbilirubinemia, kernicterus, feeding difficulties, white matter damage, seizures, and apnea, and for 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 have higher rates of neurological and developmental morbidities during childhood.

The NIH is committed to understanding the causes of preterm birth and to reduce the incidence of preterm birth, low birth weight and infant mortality and their consequences. The NICHD was the lead federal agency in planning and coordinating the Surgeon General's Conference on the Prevention of Prematurity, held in June 2008 (6, 7). Federal agencies, nonprofit organizations, professional societies, and members of the public whose lives had been affected by preterm birth all participated in formulating an agenda to heighten the visibility of preterm birth and its consequences, and to provide guidance on top priority, cross-cutting efforts to speed the identification of the causes, risk factors, and treatment of preterm labor and delivery.

Preterm birth research supported by the NICHD ranges from basic work on genetics and genomics to research regarding specific questions encountered in clinical practice, including the mechanisms, prediction and prevention of preterm delivery, optimal management of preterm labor, optimal management of the preterm neonate and the long-term implications of preterm delivery on the infant, mother and family. The NICHD supports this work through the funding of investigator-initiated applications, specific solicitations for individual grants and 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, the NICHD's intramural program includes a branch largely devoted to issues related to pregnancy, preterm birth and congenital anomalies. While the NICHD supports the bulk of NIH research in this area, other NIH institutes and centers also contribute to the overall NIH spending of $278 million, including $32 million in Recovery Act funds, for infant mortality/low birth weight/prematurity research projects in FY 2009, the last year for which we have complete data.

One of the most successful approaches for research related to prematurity is the NICHD's research networks, which allow physician scientists across the country to coordinate their work and share data. Currently, four networks focus on specific aspects of prematurity and its consequences. The first, the Maternal Fetal Medicine Units (MFMU) Network (http://www.bsc.gwu.edu/mfmu) 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 an independent data center. This network has a remarkable track record of conducting high priority clinical trials, with its findings incorporated into practice through professional societies. Work from this network includes the identification of preventative therapies for preterm birth in current practice that should be stopped as they have no impact on the preterm birth rate and on therapies that improve outcomes for preterm infants.

A second network, the Neonatal Research Network (like the MFMU, established in 1986), aims to improve the care and outcome of neonates, especially very low birthweight infants. It has led to several advances 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.

Another network is the Genomic and Proteomic Network for Preterm Birth Research (GPN/PBR). Multiple factors may determine an individual woman's risk of preterm birth including her genetic makeup and the way(s) that her genes control the expression of substances such as proteins, hormones, and infection-fighting agents. 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. Its main objective 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.

The NICHD has recently funded the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be, which will address another important aspect of preterm birth. Women for whom the current pregnancy will lead to their first delivery (nulliparas) comprise about 40 percent of the approximately 4.3 million births in the United States each year. 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. Complications during the first pregnancy affect subsequent pregnancies. This Network will study the mechanisms and predictors of adverse pregnancy outcomes in nulliparous women. The aim of this large, multicenter cohort study is to identify markers early in pregnancy that will identify women at the highest risk for preterm birth, preeclampsia, fetal growth restriction, and stillbirth. Detailed epidemiologic data, intensive clinical research assessments and biologic samples will be collected. Recent advances in genomics, proteomics and epigenetics will be applied to elucidate the mechanisms of the interplay of genetic and environmental factors. Ideally, using the findings from this study, individualized interventions can be developed aimed at preventing adverse pregnancy outcomes. Grantees will share data with investigators outside the network, to accelerate the pace of preterm birth research.

Another highly useful method for consolidating currently available scientific data and informing practice are the NIH Consensus Development Conferences. In recent years, the NIH has focused twice on the role of Cesarean delivery on preterm birthIn 2006, the NIH held the first conference, "Cesarean Delivery on Maternal Request," which found that the incidence of cesarean delivery without medical or obstetric indication has increased in the U.S. Given the risks of complications that rise with each cesarean delivery, the conferees stated that cesarean delivery on maternal request should not be recommended for women desiring several children, and should not be performed without medical indication prior to 39 weeks gestation in order to maximize lung maturity. The NIH followed up this earlier conference with another held in March 2010, "Vaginal Birth after Cesarean." The panel convened for this recent conference found that, in

women who had undergone prior cesarean delivery, while both vaginal birth after cesarean delivery and subsequent cesarean delivery have important risks and benefits for both the pregnant woman and the fetus, given the available evidence, vaginal birth after cesarean is a reasonable option for many pregnant women. The panel emphasized that both the pregnant woman and her clinician should engage in a shared decisionmaking process. The conferees' statement from the first conference, can be found at: http://consensus.nih.gov/2006/cesarean.htm, and the statement from the March, 2010, conference, at http://consensus.nih.gov/2010/vbac.htm.

Understanding the mechanism

Approximately fifty percent of preterm births occur spontaneously following the premature onset of labor, 20 percent are medically-induced deliveries due to medical conditions endangering the mother and/or fetus, and 30 percent are associated with the preterm 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 has indicated that spontaneous preterm birth has a number of possible causes (8). 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 (34-36 weeks) spontaneous preterm delivery. The physiological processes underlying these causes are currently an area of intense 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 percent of all medically-induced preterm births. Preeclampsia is a pregnancy-specific, hypertensive disorder and occurs in about four percent of all live-birth pregnancies. Researchers supported by the NICHD have shown that this disease is associated with abnormal development of the placenta, which results in reduced blood flow between the mother and the fetus (9).

NICHD-funded researchers are exploring the use of drugs to manipulate certain protective enzymes to 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 (10). 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. Therefore, 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, and thus, possible prevention of many medically-indicated preterm births.

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 percent and 8 percent, respectively. The most common causes for pPROM, currently under investigation, appear to be chronic inflammation and/or infection.

Prediction of Preterm Birth

Fetal growth restriction is a risk factor for 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, of fetal development. NICHD-funded researchers have made substantial progress in a 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. The NICHD's MFMU Network conducted a blinded, multicenter observational study of women with a prior preterm birth(11). The study showed that in high-risk women, shortened cervical length in the mid-trimester predicts early, but not later, spontaneous preterm birth. The results of this and other related studies of women at high-risk for preterm birth point to an association between cervical length and diminished cervical competence. Another NICHD-funded trial evaluated the use of cervical cerclage (a stitch around the cervix like a purse string) in high risk women with a short cervix and found in a subset that the cerclage significantly prevented preterm birth (12).

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(13). 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.

The NICHD also recently used part of its American Recovery and Reinvestment Act funding to support a grant to test a new, non-invasive technology device to study the physiological mechanism of uterine contractions through magnetic recordings. Insights from these recordings may provide innovative approaches toward suppression of preterm labor and induction of labor.

Prevention of Preterm Birth

A major advance in prevention of preterm birth was made in 2003 by a team of researchers supported by the NICHD's MFMU Network, who studied women who had had a previous

preterm delivery and therefore were considered at high risk for recurrent preterm delivery. This clinical trial compared weekly treatment by injection of a progesterone (17 alpha-hydroxyprogesterone caproate) with placebo in women at high risk for preterm birth(14). These treatments lowered the risk of a second preterm birth by one-third, the first successful treatment demonstrated to reduce the risk of recurrent preterm delivery and improve neonatal outcomes in a subset of high-risk women. The impact of this treatment was evaluated in a study published in 2005, which estimated that 10,000 preterm births could have been prevented annually if all eligible pregnant women had received it (a reduction of about two percent)(15). This preventative therapy has been translated into practice; the American College of Obstetricians and Gynecologists has recommended the use of progesterone to prevent preterm birth for women with prior spontaneous preterm birth(16). Since that time, the MFMU Network has evaluated other high risk groups, such as women with multiple gestations (twins and triplets), but thus far has found that progesterone is not beneficial in preventing preterm birth in those groups (17,18).

Research that disproves a current therapy or treatment can also provide valuable guidance to clinicians and their patients. Translational research in the 1990s found that the use of corticosteroids in pregnancies at risk of preterm birth improved the outcomes for infants born preterm, reducing the rates of breathing problems, bleeding into the brain, and problems with the intestines. However, the NICHD sponsored research that evaluated the use of repeated doses of corticosteroids, and found that they resulted in smaller birthweights and head circumferences (19). They also found a non-significant, but concerning increase in cerebral palsy in children who were exposed to four or more courses of corticosteroids (20). This study, along with an NIH Consensus Development Conference to pull together all available data, stopped the routine use of repeated courses of antenatal corticosteroids (21).

Vaginal infections have been associated in the scientific literature with preterm birth. Previous studies showed that antibiotic treatment of symptomatic bacterial vaginosis in women with a previous preterm birth reduced the risk of recurrence. Based on this evidence, many women – even those without symptoms of infection – were treated with antibiotics in an attempt to prevent preterm birth. However, a study supported by the NICHD's MFMU Network found that the use of a course of antibiotics in asymptomatic women did not decrease the risk of spontaneous delivery and did not result in improved neonatal outcomes (22). Another trial showed that screening and antibiotic treatment of all women with another type of vaginal infection (Trichomonas vaginalis) not only did not prevent preterm birth, but actually increased preterm birth (23). These trials stopped the indiscriminate use of antibiotics in pregnancy.

Evidence from European studies suggests that the omega-3 fatty acids found in cold water oily fish may reduce the chances of preterm birth. The NICHD's MFMU Network studied whether, in high risk women who are receiving weekly progesterone treatments, supplementation with two omega-3 fatty acids would result in an even greater reduction of preterm birth than progesterone alone. The trial found that omega-3 supplementation did not further reduce preterm birth, halting an ineffective intervention (24).

Antioxidants have been implicated in preeclampsia, a major cause of preterm birth. Although basic research suggested that antioxidants were beneficial, a trial evaluating supplementation

with Vitamin C and E did not prevent preeclampsia in 10,000 women in their first pregnancy, stopping the implementation of an ineffective therapy (25).

In addition to studying preventative therapies, the MFMU Network studies antenatal interventions to prevent complications in premature infants. Recently, the network identified another therapy, antenatal magnesium sulfate (Epsom salts) which, when administered to women at risk of delivering preterm, reduces the risk of cerebral palsy in surviving preterm infants by 45 percent(27). This finding was translated into clinical practice (28). Through the Network, the NIH also is supporting a new clinical trial to evaluate if antenatal corticosteroids will improve outcomes for women whose pregnancies are at risk for late preterm birth (34-36 weeks). Late preterm births account for 70 percent of preterm deliveries. The results of this trial may have substantial impact on the health of these infants.

In addition, the NICHD and the Society for Maternal Fetal Medicine will hold a workshop in February 2011 to synthesize the available information regarding conditions that result in medically indicated late preterm and early term births to determine the potential risks and benefits of continued pregnancy, the optimal gestational age for delivery (if optional), and to inform future research regarding these issues.

Caring for Preterm Newborns

Of the over 540,000 prematurely born infants in the US each year, more than five percent 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 percent of severe FGR infants develop learning disabilities and require special educational services. The NICHD is supporting research that will test the effectiveness of an intervention in the NICU for such infants, based on reducing overload on each baby's senses.

Extremely low birth weight (ELBW) infants are at increased risk for developmental and behavioral abnormalities. The NICHD Neonatal Research Network, in a large study of very small infants in 15 sites, collected detailed information on breast 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 (29).

Nitric acid is a chemical compound that is sometimes used in its gaseous form to treat infants with severe breathing problems. Inhaled nitric oxide therapy was approved by the Food and Drug Administration in 2000 to treat term and near-term infants (born after the 33rd week of pregnancy) with respiratory failure. Since its approval, researchers have examined expanding the use of inhaled nitric oxide therapy to treat premature babies born at less than 34 weeks' gestation. Studies to evaluate its safety and efficacy for these infants have had mixed results(30, 31). To better understand the potential risks and benefits of inhaled nitric oxide therapy for premature infants, the NIH will convene a Consensus Development Conference on October 27-29, 2010, to assess the available scientific evidence and come to some conclusions about its use.

Infant Mortality

Infant mortality (6.7 deaths/1,000 live births), stillbirths (6.2/1,000 live births), major birth defects (30/1000 live births) and preterm births (128/1,000 live births) are major public health priorities in the U.S (32). All of these already high rates demonstrate dramatic health disparities based on race-ethnicity with higher overall rates in African American women. Despite numerous efforts, the disparities are persisting. Researchers are attempting to identify factors to explain the disparities, evaluating genetics, socio-economic status, accessibility to health care, maternal education, and stress and disease burden, among others. However, the complexity of the interactions among these factors has made the task more difficult.

In August, 2010, the NICHD will hold a scientific workshop focused on disparities in infant mortality, stillbirth, and preterm birth. The goals of this workshop are to identify the factors associated with such disparities and to determine their relative contributions and gaps in knowledge, and to design a plan for moving research forward in both the short and long term.

Again, thanks to the Committee for your time and interest in this critical public health topic. I am pleased to answer any questions you may have.

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