INVITED EDITORIAL

World Prematurity Day: It takes an NIH village to prevent preterm birth and improve treatments for preterm infants

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Introduction

The history of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is inextricably linked to the family of former president John F. Kennedy. Two of his relatives, his sister Rosemary, who had an intellectual disability, and his son Patrick, who was born prematurely, provided personal examples of why more research was needed to advance the health of children, pregnant women, and people with disabilities.

On October 17, 1962, NICHD was established when President Kennedy signed a law that authorized the U.S. Surgeon General to "establish in the Public Health Service (PHS) an institute for the conduct and support of research and training relating to maternal health, child health and human development, including research and training in the special health problems and requirements of mothers and children and in the basic sciences relating to the processes of human growth and development, including prenatal development" (1). Forty-five years later, the institute was renamed for President Kennedy's sister, Eunice, who played a seminal role in advocating for its establishment. Almost 60 years after its founding, the current mission of the institute still reflects the original legislative language – **"to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all."**

Less than a year later, on August 7, 1963, Mrs. Jacqueline Kennedy, the First Lady of the United States, delivered a baby boy at 34 1/2 weeks' gestation who weighed 4 pounds 10 1/2 ounces. Despite being the son of the President and having access to the best medical care available in the world at that time, Patrick Bouvier Kennedy died at 39 hours of age. Author Steven Levingston has characterized this death as "The Loss that Transformed JFK" (2). It is a remarkable legacy of the Kennedy family and the science

supported by NICHD that if Patrick were born at the same gestational age today, his chances to survive and to live a normal life would be substantially higher.

Yet, despite the tremendous gains made in the care and management of preterm babies, prematurity is still a major cause of morbidity and mortality, and thus it continues to be a major focus of the institute. In the NICHD 2020 Strategic Plan (https://www.nichd.nih.gov/about/org/strategicplan), prematurity features prominently in the scientific goal "Setting the Foundation for Healthy Pregnancies and Lifelong Wellness." In addition, it is a major factor in all five cross cutting themes – health disparities, disease prevention, infectious disease, nutrition, and global health.

The Overall National Institutes of Health Research Portfolio in Preterm Birth

The National Institutes of Health (NIH) are committed to understanding the causes of preterm birth, as well as developing prevention and treatment methods to protect maternal and infant health. In fiscal year (FY) 2020, total NIH expenditures on preterm birth and newborn health research were approximately $444 million. As shown in **Figure 1**, over the past decade NIH has more than doubled its research funding in preterm birth and newborn health, from $214 million to $444 million. This expansion has extended across scientific areas within the portfolio, including prevention of preterm labor, treatment of conditions affecting preterm infants, and disparities in preterm birth rates, among others.

Twenty-three of NIH's 27 Institutes and Centers (ICs), along with the NIH Office of the Director, support research related to preterm birth (see **Figure 2**). NICHD funds the largest portion of the overall NIH portfolio with $159 million (36%). Other ICs with major investments include the National Heart, Lung,

and Blood Institute (NHLBI), the National Institute of Neurologic Diseases and Stroke (NINDS), and the National Institute on Environmental Health Sciences (NIEHS). The projects funded by each IC are aligned with each IC's unique mission. For example, NHLBI funds research in cardiovascular and respiratory disorders that affect preterm infants, and NIEHS funds research in environmental exposures related to preterm birth. Many of NIH's research efforts are collaborations across ICs, including the NIH Pediatric Research Consortium (N-PeRC), a trans-NIH initiative led by NICHD to harmonize pediatric research expertise, activities, and resources across NIH's institutes. The consortium also explores gaps in the overall pediatric research portfolio and shares best practices to advance science.

Key Research Studies

Mechanisms and Prevention of Preterm Birth

For NICHD, improving the health of newborns is fundamental to the institute's mission. NICHD has focused its efforts on research to learn more about the causes of preterm labor and birth, to improve ways to predict which women are at risk for preterm delivery, and to identify methods to reduce the number of infants born early. To this end, NICHD has aligned its research efforts to address important preterm birth knowledge gaps in its Strategic Plan Theme 3: Setting the Foundation for Healthy Pregnancies and Lifelong Wellness. Under this theme, research priorities include (*i*) understanding the human gestational clock and the potential causes of preterm birth, (*ii*) addressing the short- and long-term complications in children born preterm, (*iii*) addressing health disparities in the etiology and management of preterm birth and its consequences, and (*iv*) expanding our understanding of the etiology and management of preterm birth in people with intellectual, developmental, and physical disabilities (https://www.nichd.nih.gov/about/org/strategicplan). Health disparities research is a cross-cutting theme in the Strategic Plan, and with its newly launched STrategies to enRich Inclusion and

achieVe Equity (STRIVE) Initiative, NICHD seeks to eliminate health disparities related to maternal and infant health outcomes, including preterm labor and birth.

NICHD research emphasizes ways to prevent preterm labor and birth and to prolong pregnancy in women at risk of preterm birth. For example, scientists are exploiting the pro-gestational actions of the steroid hormone progesterone to develop selective progesterone receptor modulators (SPRMs) that can be used to promote uterine quiescence and prevent preterm birth (R01HD097279). Another NICHD study has identified the transient receptor potential vanilloid 4 (TRPV4) channel as a modulator of myometrial contractility and is establishing the TRPV4 channel as a target that, if blocked, can effectively stop preterm labor (R01HD092316). A first-of-its-kind study supported by NIEHS and NICHD found that unbalanced progesterone signals may cause some pregnant women to experience preterm labor or prolonged labor, and further suggests that progesterone receptors can be future therapeutic targets to prevent preterm birth (3). NICHD-supported scientists also recently established that a higher dose of docosahexanoic acid (DHA), an omega-3 fatty acid, is associated with lower early preterm birth rates, suggesting that screening DHA levels in pregnancy could be used as a tool to decrease risk of preterm birth (4).

An important research goal is the identification of biomarkers to predict preterm labor and preterm birth. A team of clinicians and mathematicians supported by NICHD is using a pulse oximeter to discover abnormal physiology and develop predictive algorithms (R01HD072071). A research project funded collaboratively by NICHD, the NIH Common Fund, the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of General Medical Sciences (NIGMS) has also identified differences in the vaginal bacteria that may raise the risk of preterm birth among pregnant African American women. This could be a first step toward the development of a screen for the early

identification of preterm birth risk in this population (5). Furthermore, researchers funded by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) are developing and evaluating 3D-printing methods to make inexpensive, miniature devices that will determine risk for preterm birth using a finger-prick blood sample from a pregnant woman, several weeks before contractions might occur, with the hope that this information could lead to earlier treatment initiation, if needed (R01EB027096). A study supported by NINDS is exploring the neuroprotective function of the placentally derived hormone human chorionic gonadotropin (hCG) and its receptors in a mouse model of preterm and term brain injury (R01NS112234). The National Institute on Minority Health and Health Disparities (NIMHD) is supporting a mixed-method research approach to determine how social stressors alter inflammation during pregnancy, leading to preterm birth in African American women, who have disproportionately high preterm birth rates (R01MD011575). Furthermore, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is supporting genetic studies and animal experiments to understand how mutations in the Single Immunoglobulin Interleukin-1-Related Receptor (SIGIRR) increase the risk of necrotizing enterocolitis (NEC). They will test various specific therapies that can prevent disease (R01DK117296). More recently, a study funded by the National Eye Institute (NEI) found that a very low dose of Avastin, a drug that inhibits abnormal blood vessel growth, is effective for preventing blindness from retinopathy of prematurity (ROP) in preterm infants (6).

Environmental Exposures and the Risk of Preterm Birth

NIEHS provides information about chemicals or factors in the environment to which humans are exposed that may cause adverse health effects. NIEHS also conducts research on how maternal exposure to chemicals affects pregnancy and the development of the fetus and child. NIEHS-supported scientists have examined the roles of phthalates, phenols, organophosphates, and pesticides in disorders of fetal growth and preterm birth. For example, NIEHS supports the LIFECODES pregnancy

cohort study, which has served as a resource to investigate the associations and underlying mechanisms between environmental chemical exposures in pregnancy and adverse birth outcomes. NIEHS researchers are adding to existing data by analyzing whether environmental exposures to metals alone and in combination with other chemicals cause metabolic perturbations that lead to spontaneous early delivery and sub-optimal fetal growth (ZIAES103321). Another NIEHS study is investigating whether extreme heat events increase the risk of preterm birth and early term birth and if stronger associations are observed following heat events of longer duration and greater intensity (R01ES028346). An NIEHS-funded study also showed that exposure to glyphosate — the most heavily used herbicide in the world — was associated with preterm birth and was the first study to assess the link between exposure to a glyphosate breakdown product called aminomethylphosphonic acid (AMPA) and birth outcomes (7). Another study found that exposure to two phthalates, di-n-butyl phthalate (DBP) and di-isobutyl phthalate (DiBP), were linked to lower gestational age at delivery and higher odds of preterm birth. This study was one of the largest and most detailed prospective cohort studies to investigate these associations to date (8).

Research Leading to Improved Treatment of Infants Born Preterm

NIH-supported investigators and research networks are also studying ways to improve the treatment and care of preterm infants to reduce death and disability and improve survival. For example, NICHD and NHLBI research funded through the Best Pharmaceuticals for Children Act (BPCA) program revised the off-label use of caffeine citrate, which is prescribed to treat apnea of prematurity. Researchers found that caffeine citrate may be safely given to preterm infants born earlier than 28 weeks and that the dose and duration may be higher and longer than the previous label recommendation, which only offered guidance for infants born between 28 and 32 weeks. Data collected from this work, as part of the Prematurity and Respiratory Outcomes Program study, also informed researchers that diuretic

therapy does not alleviate respiratory problems in extremely preterm infants (9). Finally, although very low birthweight infants often need blood transfusions to survive, a study co-funded by NICHD, NHLBI, and the National Center for Advancing Translational Sciences (NCATS) suggested that providing a higher red cell transfusion threshold offers no advantage for treating preterm infants (10).

NHLBI funds neonatal and pediatric lung research, including studies on bronchopulmonary dysplasia (BPD), congenital and developmental lung anomalies, and pulmonary hypertension. Preterm infants have an elevated risk of developing serious respiratory complications, and NHLBI supports research to understand their underlying mechanisms, as well as to identify risk factors and potential treatment and prevention methods. For example, patent ductus arteriosus (PDA), the delayed closure of a fetal blood vessel that limits blood flow through the lungs, is very common in preterm infants. An NHLBI-supported study will determine whether, and at what age, a preterm infant's untreated PDA is likely to close on its own and predict which preterm infants with PDA are at highest risk for PDA-associated mortality, respiratory disease, or neurodevelopmental delays (R01HL145032). Another research team will test a protein-based drug carrier for delivery of a novel peptide-based antagonist for sFlt-1, which could have major therapeutic benefits for patients with preeclampsia, a major cause of premature birth (R01HL137791). Moreover, NHLBI-supported researchers discovered a possible cell-based therapy involving c-KIT-positive endothelial progenitor cells, which are common in neonatal lungs and aid in the formation of capillaries and air sacs in the lungs, to help stimulate lung development in premature infants with BPD (11). Research funded by NHLBI has also shown that premature newborns who received regular vitamin D supplements had a lower risk of wheezing than those who did not receive supplements. These findings may help improve clinical care to prevent the complications of respiratory diseases in newborns.

Clinical Research Infrastructure to Support Preterm Birth Research

NICHD's Division of Extramural Research

Clinical Trial Networks and Resources

When multiple research and clinical centers come together to form a clinical research network, they can advance maternal and neonatal care by studying large numbers of patients to provide answers more rapidly and rigorously than individual research teams acting alone. The depth of research experience, range of populations, and collaborative efforts found in research networks allows NIH to address complex research questions related to preterm birth. Moreover, research networks provide the infrastructure to launch research efforts quickly in the case of public health emergencies such as the COVID-19 pandemic. For example, the GRAVID study, launched in 2020 through NICHD's Maternal-Fetal Medicine Units (MFMU) Network, showed that pregnant women who experienced severe symptoms of COVID-19 had a higher risk of cesarean delivery, postpartum hemorrhage, hypertensive disorders of pregnancy, and preterm birth, compared to asymptomatic COVID-19 patients (12).

NICHD's Neonatal Research Network (NRN) is a collaborative network of neonatal intensive care units across the United States focused on research to advance the care of vulnerable newborns, particularly preterm and extremely low birth weight (ELBW) infants. Among the areas addressed by the NRN are studies on preterm birth complications and outcomes, the prevention of sepsis, the prevention or treatment of chronic lung disease such as BPD and pulmonary hypertension, asphyxia, anemia, intraventricular hemorrhage, and outcomes and resource requirements for very low birth weight (VLBW) infants. The NRN pioneered research on hypothermia as a treatment for birth asphyxia. The NRN also conducted trials demonstrating that vitamin A supplementation slightly decreased the risk of chronic lung disease in ELBW infants. In addition, the NRN has established a database of low birthweight and extremely premature infants born alive in NRN centers. These data are analyzed to find associations

and trends in baseline data, treatments, and infant outcomes and to develop future NRN trials. They also form the basis of the NRN's Extremely Preterm Birth Outcomes Tool (https://www.nichd.nih.gov/research/supported/EPBO), which gives physicians predictive estimates of infant mortality and morbidity using five key factors: gestational age, birth weight, sex, singleton/multiple birth, and whether the mother received corticosteroids before delivery. Ongoing NRN studies related to preterm birth and respiratory diseases in infants are shown in **Table 1**.

Among NICHD's major programs and projects on pregnancy outcomes is the MFMU Network, which supports clinical trials designed to reduce maternal pregnancy complications and fetal and infant mortality and morbidity. A recent MFMU Network study indicated that an antibody treatment in early pregnancy for women infected with cytomegalovirus does not appear to reduce the risk of infection or death among their newborns (13). MFMU Network researchers are studying the effectiveness of pessaries in different subgroups of women at risk for preterm birth and observing opioid prescribing patterns after delivery. Past MFMU Network studies have provided key findings on outcomes of infants induced at 39 weeks, compared to waiting for the onset of labor. Its studies have also shed light on the costs and effectiveness of antenatal corticosteroids and on therapies for subclinical hyperthyroidism. Ongoing MFMU Network studies related to preterm birth are shown in **Table 2**.

Another NICHD network, the Pediatric Trials Network (PTN), which is funded through the BPCA, comprises over 100 clinical research sites studying the formulation, dosing, efficacy, and safety of drugs, as well as the development of medical devices, used in pediatric patients. The PTN primarily conducts trials with off-patent drugs that are lacking data in pediatric populations. One PTN study, Diuretic Safety of Furosemide in Premature Infants at Risk of Bronchopulmonary Dysplasia, is assessing the safety and preliminary effectiveness of furosemide, which is often used to prevent BPD in premature infants

(NCT02527798). Another PTN study seeks to describe the safety of sildenafil for use in premature infants at risk of BPD and to determine its preliminary effectiveness and pharmacokinetics (NCT 03142568). Data collected from these trials can help regulators to revise drug labels for safer and more effective use in treating diseases and conditions that affect premature infants.

Another NICHD network, the Global Network for Women's and Children's Health Research, comprised of eight international-domestic partner sites, also performs research related to preterm birth. One recently completed prospective, randomized, placebo-controlled, double-blinded, multi-center clinical trial examined whether low-dose aspirin initiated between 6 0/7 weeks to 12 6/7 weeks gestation reduced the risk of preterm birth (14). The clinical trial, which involved more than 11,000 women in several low- and middle-income countries, found that women taking daily low-dose aspirin were 11% less likely to deliver before the 37th week of pregnancy, compared to those given the placebo (14).

NICHD also conducted the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) to study nulliparous women, those for whom the pregnancy at the time of the study would lead to the woman's first delivery. Potential adverse pregnancy outcomes among nulliparous women are less predictable because they have not given birth before; no prior data exist on how they respond to pregnancy. NuMoM2b began in 2010 and compiled data on more than 10,000 racially, ethnically, and geographically diverse participants. Data entry began in the 6th week of pregnancy and continued through delivery. Collected data include interviews, questionnaires, clinical measurements, patient charts, and biological specimens (15). The primary outcome of the study was to determine which women had a high risk of delivering prematurely (16, 17).

NICHD also supports a centralized resource for researchers across the world to share de-identified data from completed studies funded by NICHD. This publicly available resource, known as the Data and Specimen Hub, or DASH (https://dash.nich.nih.gov) facilitates the rapid testing of hypotheses related to preterm birth and preterm infants, among its 49 study topics. In addition, the DASH site serves as a portal to request linked biospecimens that include maternal blood, breast milk, and amniotic fluid, among others.

NICHD's Division of Intramural Research

Approximately 14% of NICHD's overall budget supports research performed by our intramural investigators.

Perinatology Research Branch (PRB)

The NICHD Perinatology Research Branch (PRB) has an extensive clinical research center in conjunction with Wayne State University, which serves a large population of mostly minority women in Detroit, Michigan. PRB focuses on the study of the causes of preterm birth and mechanisms of disease and conducts clinical studies to improve the prediction, treatment, and prevention of preterm birth.

Two-thirds of preterm births occur after the spontaneous onset of labor, whereas the remainder are medically indicated because of maternal or fetal complications such as preeclampsia and fetal growth restriction (18). The traditional paradigm that has governed the study of preterm labor is that term and preterm labor are similar processes that differ in the gestational age when labor begins. However, investigators at PRB have proposed that preterm labor is a syndrome resulting from multiple pathologic events that activate "the common pathway of parturition" (myometrial contractility, cervical ripening, and membrane/decidual activation) (19). This framework has served as the basis for a research agenda

in PRB to identify biomarkers and interventions to treat and prevent each of the causes of the preterm parturition syndrome.

For example, a decline in progesterone action has been proposed to lead to cervical ripening clinically manifested as a sonographic short cervix in the mid-trimester, which is the most powerful risk factor for spontaneous preterm delivery (20). Through a large international randomized clinical trial and subsequent systematic reviews and meta-analyses, PRB investigators have found that vaginal progesterone reduces the risk of preterm birth by 38% in women with a sonographic short cervix. This is associated with a lower rate of neonatal morbidity/mortality (21, 22). Furthermore, economic studies indicate that universal cervical length assessment coupled with treatment with vaginal progesterone is cost effective and can save the United States approximately $500 million per year. This strategy is also effective in women with a previous preterm birth and a short cervix and is as effective as cervical cerclage (23). Moreover, to implement this work in clinical practice, a calculator has been developed to calculate the risk of preterm delivery incorporating cervical length, as well as maternal characteristics such as weight, height, parity, and gestational age (24).

Intra-amniotic infection is present in one of every four women with spontaneous preterm birth and is causally linked to preterm labor (25). These infections are subclinical in nature in over 80% of cases and are caused by microorganisms normally present in the lower genital tract of most pregnant women (e.g., *ureaplasma* species) (26, 27). PRB investigators have identified the microorganisms involved in intra-amniotic infection using cultivation and molecular microbiologic techniques. They have established that ascending infection from the lower genital tract is the most common pathway of infection (28). Moreover, microorganisms and their products can stimulate an inflammatory response in the chorioamniotic membranes (i.e., chorioamnionitis) and can invade the fetus causing a fetal

311 inflammatory response syndrome (FIRS) (29). As such, investigators at the PRB have developed methods
312 for the rapid diagnosis of intra-amniotic infection/inflammation based on amniotic fluid analysis (30, 31)
313 and have recently shown that contrary to the long-held view that intra-amniotic infection/inflammation
314 could not be treated, antimicrobial agents administered to pregnant women can eradicate intra-
315 amniotic infection/inflammation and be associated with delivery near term in patients with preterm
316 labor and intact membranes (32), preterm pre-labor rupture of membranes (33, 34), and cervical
317 insufficiency (32, 35). PRB investigators have also shown that long-term complications of prematurity
318 such as BPD (36, 37) and cerebral palsy are more frequent in patients with intra-amniotic
319 infection/inflammation (38). Experimental evidence also suggests that anti-inflammatory treatment with
320 nanodevices can reduce neuroinflammation and its clinical manifestations (39).
321
322 Recent work has also shown that a subset of patients with preterm labor have sterile intra-amniotic
323 inflammation (40) and that the mechanism of labor involves activation of the inflammasome and
324 blocking the NLRP-3 inflammasome can prevent preterm delivery (41, 42). Ongoing investigations are
325 addressing the role of other mechanisms of disease such as the breakdown of maternal-fetal tolerance
326 (43). PRB investigators have also recently reported that ablation of regulatory T cells in late pregnancy
327 that promote maternal-fetal tolerance can result in spontaneous preterm birth and that adoptive
328 transfer prevents spontaneous preterm birth (44). These observations are clinically relevant given that
329 placental lesions consistent with maternal anti-fetal rejection are the most common placental lesions
330 present in patients with late spontaneous preterm birth, which causes 70% of all preterm births (45).
331
332 The identification of biomarkers using amniotic fluid and maternal blood biomarkers (transcriptomics,
333 proteomics, and metabolomics) to predict preterm delivery is a major focus of the PRB (46).
334 Importantly, a set of microRNAs from peripheral blood from the first trimester can identify patients at

risk for spontaneous preterm delivery with a sensitivity of 89% and a specificity of 71% (46). Transcriptomic signatures in amniotic fluid and maternal blood can predict the development of preterm, pre-labor rupture of membranes, as well as impending preterm delivery within 24 hours (70% sensitivity at a 10% false positive rate) (47, 48).

Division of Intramural Population Health Research (DIPHR)

NICHD's DIPHR uses a life-course approach to study population health and disease outcomes. Multiple recent studies conducted by DIPHR investigators have included pregnant women and their children and followed them through birth and beyond. Noteworthy findings on preterm birth can be categorized into four areas of research. First, select studies have examined the role that maternal health plays in preterm birth. Specifically, DIPHR investigators have shown that a higher odds ratio of preterm birth (less than 37 weeks of gestation) is associated with various psychiatric disorders, including maternal depression (OR = 1.31, 1.23–1.40), anxiety disorder (OR = 1.68, 1.41–2.01), bipolar disease (OR = 1.54, 1.22–1.94), and unspecified (OR = 1.52, 1.41–1.64) (49). Furthermore, despite the heterogeneity in autoimmune diseases, DIPHR investigators observed elevated risks of preterm birth with type 1 diabetes mellitus (RR: 3.52; 95% CI: 3.17, 3.91), systemic lupus erythematosus (RR: 2.90; 95% CI: 2.42, 3.48), and Crohn's disease (RR: 1.84, 95% CI: 1.37, 2.49) (50). A second area of research has explored how community and maternal characteristics affect preterm birth. For example, DIPHR investigators have shown that increasing state-level income inequality, as measured by a rise in the Gini coefficient (a measurement of income inequality) in the year prior to a birth, is associated with a higher risk (OR: 1.07, 95 % CI: 1.04, 1.11) of preterm birth between 22 and 37 weeks of gestation, independent of maternal demographic factors and health behaviors (51). A third line of research has focused on how air pollution (e.g., sulfur dioxide, ozone, nitrogen oxides, nitrogen dioxide, carbon monoxide, and particles < 10 microns) contributes to prematurity. In the general population of pregnant women, exposures to

pollutants across different time windows have been shown to be associated with increased risk for both premature rupture of membranes (52) and preterm birth (53).

NICHD-supported researchers have also found that pregnant women with asthma may be at greater risk of preterm birth when exposed to high levels of certain traffic-related air pollutants. The researchers observed an increased risk associated with both ongoing and short-term exposure to nitrogen oxides and carbon monoxide, particularly when women were exposed to those pollutants just before conception and in early pregnancy. This study was also the first to examine whether exposure to air pollution before conception might affect later pregnancy (54). The investigators found that pregnant women with asthma face higher risks of preterm birth after acute exposure to most air pollutants at both earlier (weeks 23, 26, and 29) and later stages (weeks 34-36) of gestation (54).

Finally, DIPHR researchers have highlighted the implications of premature birth for subsequent health outcomes. For example, children born preterm have been found to be at increased risk of neurocognitive (55) and developmental problems (56).

SARS-CoV-2 infection during pregnancy and preterm birth

Infection with SARS-CoV-2 during pregnancy is associated with an increased rate of preterm birth. The greater the severity of SARS-CoV-2, the higher the risk of preterm birth, which is thought to be related to an increase in medically indicated, rather than spontaneous, preterm birth (57). A systematic review and meta-analysis also indicated an association between SARS-CoV-2 infection during pregnancy and the odds of preeclampsia (pooled odds ratio 1.58, 95% CI 1.39-1.80; P<0.001; I^2=0%; 11 studies) (58). This association was also found for preeclampsia with severe features, eclampsia, and HELLP syndrome.

Importantly, both symptomatic and asymptomatic SARS-CoV-2 infections significantly increase the risk of preeclampsia, although the risk is greater for symptomatic illness (odds ratio for symptomatic illness: 2.11, 95% CI 1.59-2.81 vs. odds ratio asymptomatic illness: 1.59, 95% CI 1.21-2.10). The relationship between SARS-CoV-2 infection and preeclampsia appears to be causal in a subset of cases; moreover, the median interval between SARS-CoV-2 infection and preeclampsia has been reported to be 3.7 weeks and has a dose response relationship.

The link between SARS-CoV-2 infection and preeclampsia has been attributed to endothelial cell dysfunction, intravascular inflammation, and activation of the hemostatic system. To address the issue more rigorously, NICHD recently organized a workshop that included both intramural and extramural investigators to propose a consensus definition of SARS-CoV-2 infection of the placenta (59). A graded classification was proposed that ranged from proven infection requiring detection of viral replication and localization of the virus in the placenta using molecular techniques to detect the virus and morphologic methods to establish the location of the virus in the placenta. This classification is intended to complement World Health Organization recommendations to assess vertical transmission of the virus, which has been reported to occur in approximately 3.3% of what?.

Conclusions

In summary, NIH is devoting significant resources to prevent preterm birth by identifying novel biomarkers to detect at-risk pregnant persons and to develop new treatment strategies. In addition, a multi-pronged approach is being used to improve the care of preterm newborns. These efforts involve almost all NIH institutes and centers, who work independently and collaboratively, to support investigators all over the world. It truly takes a village to make an impact on the serious problem of

prematurity. We look forward to a time when advances in research will obviate the need to acknowledge World Prematurity Day.

Note: Further details on the NIH-funded grants listed as R01 numbers in this paper may be found online at NIH RePORTER (https://reporter.nih.gov/). Further details on clinical trials that are indicated by NCT numbers may be found online at ClinicalTrials.gov.

Acknowledgments: The authors would like to thank Sarah Glavin and Niteace Whittington from the NICHD Office of Science Policy, Reporting, and Program Analysis for their extensive portfolio analysis of extramural NIH research grants focusing on the prevention of prematurity and the treatment of preterm infants.

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726 **Table 1.** Ongoing NICHD Neonatal Research Network (NRN) studies related to preterm birth and
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Ongoing NRN Study	Brief Description
The Generic Data Base Study (GDB): Survey of Morbidity and Mortality in Very Low Birth Weight (VLBW) Infants NCT00063063	The GDB is a registry of very low birth weight infants born alive in the NICHD NRN centers. The GDB collects observational baseline data on both mothers and infants, and the therapies used and outcomes of the infants. The information collected is not specific to a disease or treatment (i.e., it is "generic"). Data are analyzed to find associations and trends between baseline information, treatments, and infant outcome, and to develop future NRN trials. The GDB serves as the 'backbone' of the Extremely Preterm Birth Outcomes Tool (EPBO).
Hydrocortisone for BPD NCT01353313	This is a randomized controlled trial of the effect of hydrocortisone on survival without bronchopulmonary dysplasia (BPD) and on neurodevelopmental outcomes at 22-26 months of age in intubated infants < 30 weeks gestation age. Specifically, this study is testing the safety and efficacy of a 10-day course of hydrocortisone for infants who are less than 30 weeks estimated gestational age and who are intubated at 14-28 days of life; it will determine if hydrocortisone improves infants' survival without moderate or severe BPD and is associated with improvement in survival without moderate or severe neurodevelopmental

	impairment at 22-26 months corrected age.
Hydrocortisone for BPD Follow-Up (HYBRiD) NCT01353313	This study is a follow-up study of infants enrolled in the Hydrocortisone for BPD Trial (NCT01353313) (see above) at 5-6 years corrected age to assess functional developmental and respiratory outcomes at early school age.
Budesonide in Babies (BiB) NCT04545866	This is a Phase 3, randomized, masked, active-controlled, multicenter trial designed to determine whether early intratracheal administration of a combination of budesonide with surfactant, as compared to surfactant alone, will reduce the incidence of physiologic bronchopulmonary dysplasia (BPD) or death by 36 weeks' post-menstrual age in extremely preterm infants.
Moderately Preterm Infants with Caffeine at Home for Apnea (MoCHA) NCT03340727	This study is evaluating the effect of continuing treatment with caffeine citrate in the hospital and at home in moderately preterm infants with resolved apnea of prematurity on days of hospitalization after randomization.

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731 **Table 2.** Ongoing NICHD Maternal-Fetal Medicine Units (MFMU) Network studies related to preterm
732 birth.
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Ongoing MFMU Network Study	Brief Description
A Trial of Pessary and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix (PROSPECT) NCT02518594	This study is a randomized trial of 630 women evaluating the use of micronized vaginal progesterone or pessary versus control (placebo) to prevent early preterm birth in women carrying twins and with a cervical length of less than 30 millimeters.
A Randomized Trial of Pessary in Singleton Pregnancies with a Short Cervix (TOPS) NCT02901626	The study is determining whether the Arabin pessary is a useful intervention of preterm birth at less than 37 weeks in women with a singleton gestation and a short cervix.
The Maternal-Fetal Medicine Units (MFMU) Prematurity Registry	This is an observational cohort study of obstetrical determinants of preterm delivery and neonatal outcome.

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Figure 1: NIH Expenditures Research on Preterm Birth, Low Birth Weight, and the Health of the Newborn, 2011-2020

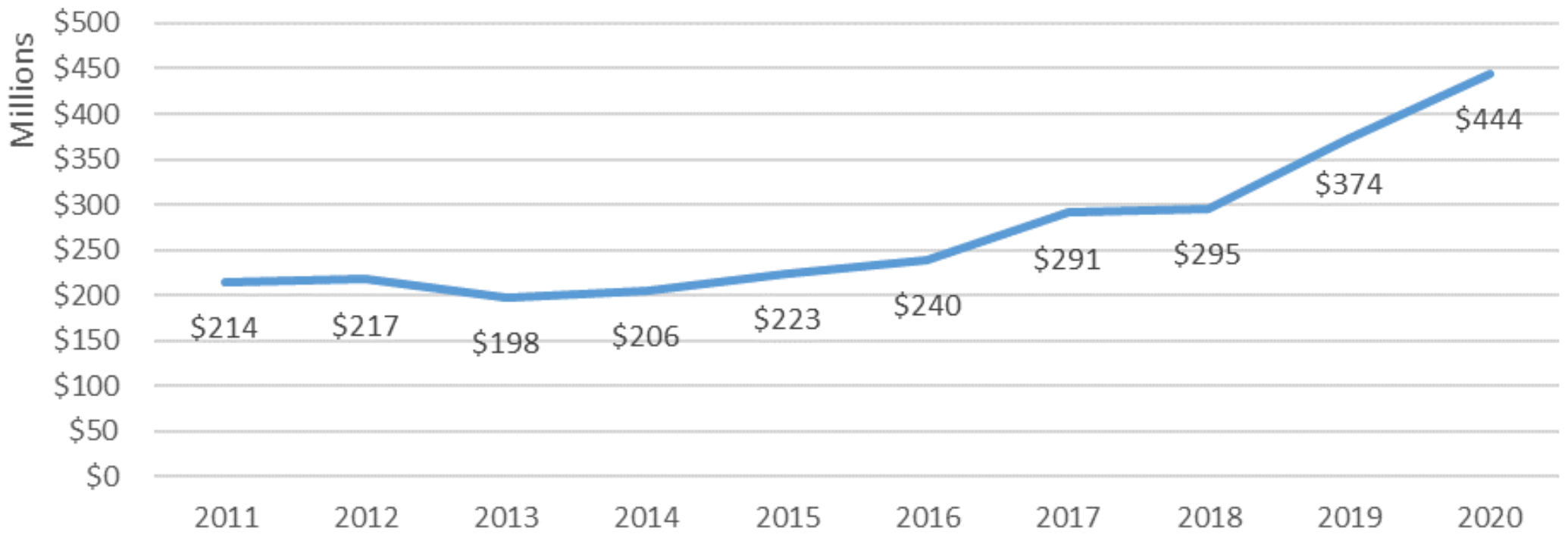

Figure 2: NIH Expenditures Research on Preterm Birth, Low Birth Weight, and the Health of the Newborn, by Institute or Center, FY 2020