

EDITORIAL

World Prematurity Day 2020: “Together for babies born too soon—Caring for the future”

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World Prematurity Day (formerly known as International Prematurity Awareness Day) was initiated by the European Foundation for the Care of Newborn Infants (EFCNI) together with associated partner organizations, and since 2009 has been celebrated on the 17th of November every year. Approximately one in every ten newborns is born prematurely (that is, before completing 37 weeks of gestation), amounting to an estimated global 15 million new preterm births every year (28). The objective of World Prematurity Day is to raise awareness about preterm birth and the concerns of both preterm born infants and their families (16, 18). Complications of preterm birth are the leading cause of death in children under five years of age (25). Those infants who survive preterm birth are at risk for a range of severe complications in the neonatal period (the first four weeks of postnatal life). Furthermore, survival of preterm born infants comes at the expense of health in adulthood (8–10, 38, 44). The early and late complications of preterm birth include respiratory, cardiovascular, gastrointestinal and renal disease, as well as diabetes and metabolic syndrome, and neurodevelopmental and cognitive disorders. The global theme for World Prematurity Day 2020 is “Together for babies born too soon—Caring for the future,” and this year’s theme highlights the need for coordinated interaction between healthcare professionals (including scientists), parents, caregivers, and policy makers (50) to address the increasingly worrisome burden of preterm birth (4, 13–15, 41, 45). Two Editorials accompany this Editorial to observe World Prematurity Day 2020 in the pages of the *American Journal of Physiology-Lung Cellular and Molecular Physiology*. In the first of these partner Editorials (50), Ms. Silke Mader, Chair of the Executive Board and cofounder of EFCNI, headquartered in Munich, Germany, together with EFCNI Head of Scientific Affairs, Dr. Johanna Kostenzer, and EFCNI Senior Medical Director, Dr. Luc J. I. Zimmermann, have outlined a multidisciplinary approach to tackle bronchopulmonary dysplasia (BPD), the most common complication of preterm birth. In a second partner Editorial (24), Drs. Ornella Lincetto and Anshu Banerjee, representing the leadership of the Department of Maternal, Newborn, Child and Adolescent Health and Aging at the World Health Organization in Geneva, Switzerland, highlight strategies for the global improvement of survival and quality of life of infants born preterm.

Developmental biologists, physiologists, and clinician-scientists who manage preterm born infants endeavor to understand the pathophysiological basis of the complications of preterm birth. This facilitates the development of new or improved strategies for the medical management of preterm born infants. That there are specific clinical complications of preterm birth has been recognized in the scientific literature for over 150 years. As early as 1837, Dr. Charles-Michel Billard described fatal “gangrenous enterocolitis” in a newborn (5), subsequently referred to as *L’entérocélite ulcéro-nécrotique* (ulcero-necrotic enterocolitis) in the French literature in 1939 (39), and necrotizing enterocolitis (NEC) in the English literature in 1963 (46). Over 150 years later, a definitive cause for NEC remains unclarified (35). Another key long-recognized complication of preterm birth includes retinopathy of prematurity (ROP), first described by Dr. Theodore L. Terry in 1942 (43). Together, NEC and ROP represent two common and serious extra-cardiopulmonary complications of preterm birth.

Preterm birth is also associated with multiple serious cardiopulmonary complications. These may include apnea of prematurity (11), neonatal respiratory distress syndrome (48), BPD (3, 17, 34), pulmonary vascular disease and pulmonary hypertension associated with BPD and preterm birth (30), and patent ductus arteriosus (12). It is clear from monitoring trends in publications over the past 40 years that there is increasing interest (evident from increasing numbers of publications that have emerged over the past 40 years) in studies on both the clinical management and the pathophysiological basis of the cardiopulmonary complications of preterm birth (Fig. 1). Indeed, the number of publications on BPD—the most common cardiopulmonary consequence of preterm birth—in the year 2019 (Fig. 1A) approximated the number of publications on both ROP (Fig. 1D) and NEC (Fig. 1E), which represent two commonly encountered extra-cardiopulmonary complications of preterm birth. A fourfold increase in the number of studies published in the year 2019 (the year of the 11th World Prematurity Day) on pulmonary hypertension associated with BPD is also evident (Fig. 1F), compared with the year 2009 (the year of the 1st World Prematurity Day). It is tempting to speculate that advocacy by organizations such as the EFCNI has contributed to the drive to understand and manage emerging aspects of the complications of preterm birth, such as BPD-associated pulmonary hypertension.

Of the 694 publications on BPD that appeared in the year 2019 (Fig. 1A), 16 appeared in the *American Journal of Physiology-Lung Cellular and Molecular Physiology*, a well-

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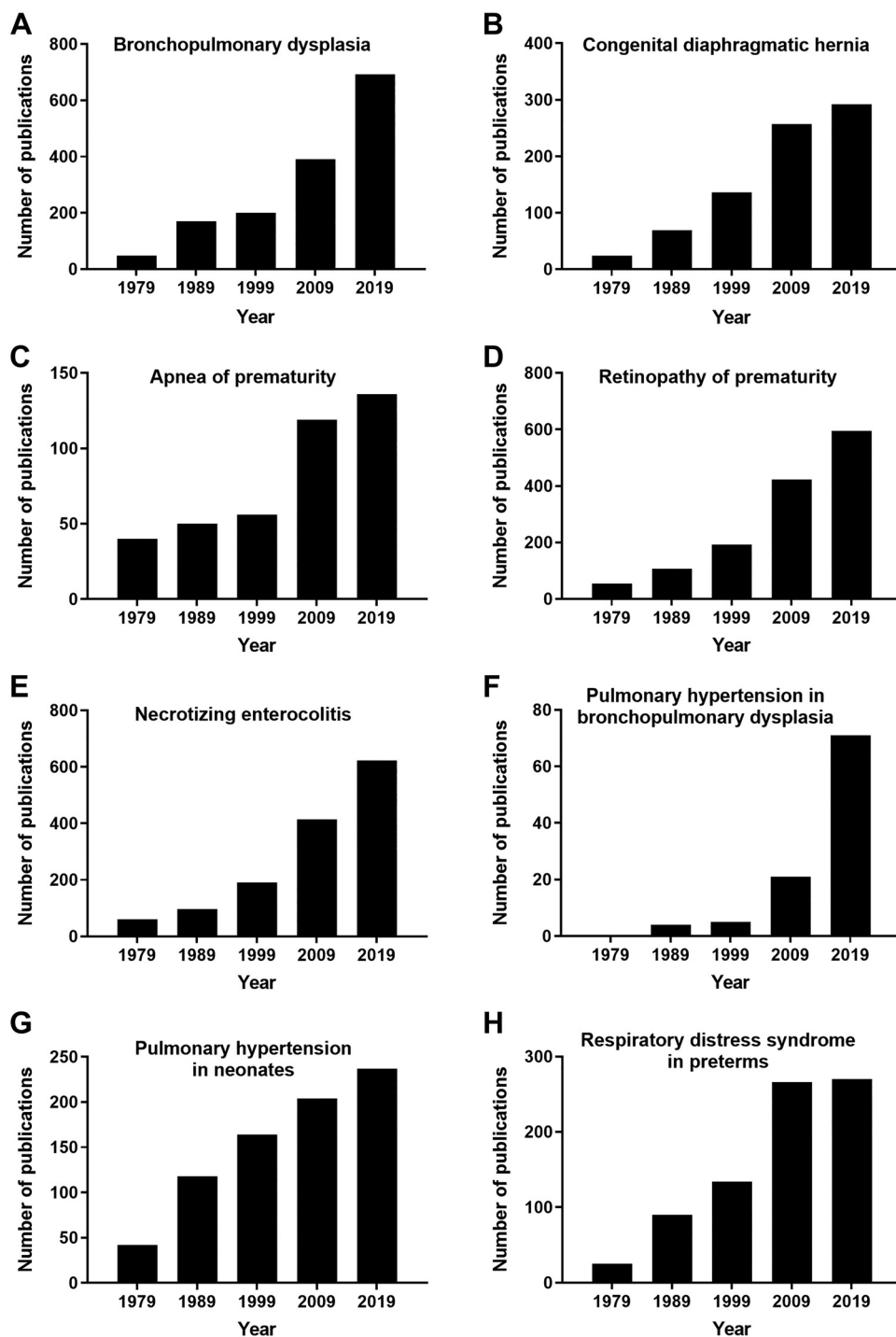


Fig. 1. Trends in the publication of articles addressing pathologic aspects of preterm birth. The number of publications that appeared in MEDLINE in the stated year are listed for bronchopulmonary dysplasia (A), congenital diaphragmatic hernia (B), apnea of prematurity (C), retinopathy of prematurity (D), necrotizing enterocolitis (E), pulmonary hypertension in bronchopulmonary dysplasia (F), pulmonary hypertension in neonates (G), and respiratory distress syndrome in preterm infants (H). Note that the last two dates on each abscissa, 2009 and 2019, are the dates of the first and eleventh World Prematurity Day, respectively.

recognized repository of knowledge about the physiological basis of cardiopulmonary complications of preterm birth. Our *Journal* publishes a comprehensive biennial review of all studies that address both the physiology of normal lung development, as well as the pathophysiology of clinical cardiopulmonary entities associated with preterm or term birth. These entities include BPD (publication trends in Fig. 1A); congenital diaphragmatic hernia (publication trends in Fig. 1B) and apnea of prematurity (publication trends in Fig. 1C). Also addressed in the biennial review are pulmonary

hypertension either specifically associated with BPD (publication trends in Fig. 1F), or in neonates in general, which would include persistent pulmonary hypertension of the newborn (publication trends in Fig. 1G); as well as neonatal (or infant) respiratory distress syndrome (publication trends in Fig. 1H). The most recent such biennial review was published in 2019 (23).

Our *Journal* regularly publishes Research Articles that address topical themes related to the causes and consequences of preterm birth. For example, recent articles have considered

the utility of combining surfactant and steroid therapy in large animal models of BPD (19), the utility of clinical-grade extracellular vesicles to manage lung injury in rat models of BPD (37), the genetic basis of sex-specific differences in neonatal hyperoxic lung injury (49), and umbilical cord proteomics to predict BPD-associated pulmonary hypertension (20). It is now recognized that there is a pressing need both for the establishment of new or refined animal models that better recapitulate the pathophysiological sequelae of preterm birth (29, 32), and for the development of new methodological approaches to clarify the histopathological characteristics of cardiopulmonary disease present in preterm infants today (1). With these ideas in mind, our *Journal* has recently published articles that report the refinement of in vivo modeling of BPD in experimental animals other than the mouse, for example, in rabbits (40). Our *Journal* is also home to recent reports that include pioneering developments in experimental methodology to study lung structure and function, for example, the three-dimensional reconstruction of the pulmonary vasculature from serial tissue sections (31). In addition to the publication of Research Articles, our *Journal* promotes discourse on topical themes in studies on preterm birth, such as the emerging role of the microbiome (22) through Editorial Focus articles (21, 47), which have discussed Research Articles on the microbiome of neonates that were recently published in our *Journal*.

To attract the submission of manuscripts that address topical themes of current special interest, our *Journal* has issued a number of Calls for Papers. Several of these Calls for Papers are relevant to the physiology of stunted lung development associated with preterm birth. Our Call for Papers “Deconstructing Organs: Single-Cell Analyses, Decellularized Organs, Organoids, and Organ-on-a-Chip Models” highlights the interrogation of clinical samples with new, state-of-the-art molecular approaches, and encourages the development of new in vitro models of pathophysiological processes to study pathophysiological processes. These are two priority areas in studies on lung disease in preterm infants (23). Another recently launched Call for Papers “Lung Diseases in Reverse Translation: Bedside to the Bench” showcases clinical problems, including those associated with preterm birth, for which no adequate physiological explanation exists, and aims to stimulate bench investigations to address those deficits in our knowledge. Information on these Calls for Papers, as well as others that address extracellular vesicles, cell senescence, and circadian rhythms in lung physiology—all of which are topical issues in the area of lung developmental (patho)physiology (23)—may be found at <https://journals.physiology.org/Calls>.

It is clear from the trends in the data presented in Fig. 1 that studies on the causes and consequences of preterm birth have picked up pace over the past decade. However, there is tremendous scope for further discovery. 1) The physiological basis of stunted lung development associated with preterm birth remains poorly understood, and an understanding of the pathophysiological pathways at play would open new opportunities for both prevention and medical management of affected infants. 2) The expansion of the currently limited pharmacological armamentarium available to the neonatologist with which to manage preterm birth remains a priority (27). 3) The use of oxygen in neonatal resuscitation (7), and in the management of preterm birth (2), as well as in animal models of BPD (32, 33) continues to be challenged and refined. 4) The delineation of new antenatal factors—and a better appreciation of the impact of antenatal

factors already identified (42)—that contribute to the causes and consequences of preterm birth will aid in the future prevention of preterm birth, and limitation of its sequelae. 5) Improved disease phenotyping (26), including the use of biomarkers (36), will facilitate the personalized management of affected infants. 6) Experimental studies and long-term clinical follow-up of adult survivors of preterm birth will reveal the role played by preterm birth in predisposition to adult lung disease (6, 44). These represent just six of a multitude of areas in experimental and clinical studies on preterm birth that demand further investigation. There remains much important and exciting work to be done!

The global theme for World Prematurity Day 2020 is “Together for babies born too soon—Caring for the future.” Through the dissemination of knowledge and discoveries about the pathophysiology of the causes and consequences of preterm birth, the *American Journal of Physiology-Lung Cellular and Molecular Physiology* is an important partner in the team of healthcare professionals (including lung physiologists), together with parents, caregivers, and policy makers, that work together for babies born too soon.

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AUTHOR CONTRIBUTIONS

M.G. prepared figure; M.G. and R.E.M. drafted manuscript; M.G. and R.E.M. edited and revised manuscript; M.G. and R.E.M. approved final version of manuscript.

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