JAMA Network Open

Invited Commentary | Environmental Health

Is the Environment Associated With Preterm Birth?

Ruth A. Etzel, MD, PhD

+ Related article

Author affiliations and article information are listed at the end of this article.

Prevention of premature birth is a major public health priority. The most recent US data indicate that the rate of premature birth increased in 2018 for a fourth consecutive year to 10%. Worldwide, an estimated 10.6% of births were premature in 2014, the most recent year for which data are available.[1] Babies born before 37 weeks' gestation are at a higher risk of neurodevelopmental disorders and respiratory and gastrointestinal impairments that may persist into adulthood.[2]

A variety of individual risk factors for preterm birth have been identified, and substantial funding and carefully designed research efforts have been undertaken to modify these risk factors. Despite these efforts, a sustained reduction in the rate of preterm birth in the United States has yet to be achieved. A Cochrane review identified 3 interventions that showed clear evidence of benefit to prevent pregnant women from giving birth early, including midwife-led continuity models of care for all women, screening for lower genital tract infections for pregnant women, and zinc supplementation for pregnant women without systemic illness.[3] In 2007, the Institute of Medicine summarized the potential role of environmental toxicants in preterm birth and asserted that the vast number of pollutants to which a woman may be exposed had never been considered in an investigation of preterm birth.[4] During the years that followed the Institute of Medicine report, additional investigations were completed, bolstering the evidence that maternal prenatal exposures to air pollution, lead, some pesticides, perfluoroalkylated and polyfluoroalkylated substances, and phthalates may contribute to the risk of preterm birth. To date, these have not been evaluated contemporaneously in a single investigation of preterm birth.

The study by Zhang et al[5] provides additional documentation that phthalates may be associated with preterm birth. They describe the findings of a prospective preconception cohort of 419 mothers and 229 fathers who were recruited from a large academic fertility center. More than 40% were older than 35 years, more than 80% were categorized as white, and more than 60% had completed college. The study investigators obtained urine samples before conception and measured 13 metabolites of phthalates and phthalate substitutes. Phthalates, a group of synthetic chemicals that are endocrine disruptors, are widely used to soften plastics, and nationally representative data from the Centers for Disease Control and Prevention have documented that virtually every individual in the United States has evidence of phthalates in their bodies. In this cohort from Boston, Massachusetts,[5] 8% of infants were born preterm. The most important finding of the study was that after controlling for other known risk factors (including assisted reproductive technology), the concentration of the sum of four di(2-ethylhexyl) phthalate (DEHP) metabolites in maternal urine was associated with a 50% increase in the risk of preterm birth (risk ratio, 1.50; 95% CI, 1.09-2.06). After adjustment for prenatal concentrations of these DEHP metabolites, the association of maternal preconception DEHP metabolites with premature birth remained robust, suggesting that mothers' exposures to DEHP before conception may be a risk factor for preterm birth.

Previously, it had been reported that exposure to phthalates and their metabolites during pregnancy was associated with preterm birth,[6,7] but the study by Zhang et al[5] appears to be novel in describing an association between preconception exposure to specific phthalate metabolites and preterm birth. Food can be a major source of phthalates such as DEHP; poultry, oils, fats, and cream have consistently high concentrations.[8] Other foods, such as fruits and vegetables, eggs, yogurt, milk, pasta, noodles, and rice, have consistently low phthalate concentrations. However, intervention studies have documented that it is very difficult to reduce phthalate concentrations by implementing

dietary changes, in part because of widely variable concentrations in bread, cereal, spices, and seafood.[8]

The findings reported in the study by Zhang et al,[5] if replicated by others, along with the emerging body of toxicologic and epidemiologic evidence showing an association between prenatal exposures to environmental chemicals and preterm birth, suggest that reducing risk factors for preterm birth during the first trimester of pregnancy may be too late. The World Health Organization and other scientific bodies have proposed that the public health community focus additional attention on ensuring optimal maternal health during the period before conception. Women of childbearing age are already advised to routinely take folic acid supplements before conception; efforts to reduce or eliminate exposures to chemicals found in everyday environments could also begin before conception. Many reproductive toxicants are present in air, water, food, and products in the home; it is difficult to prescribe specific actions that predictably eliminate these ubiquitous chemicals. Certain prevalent exposures, such as those from air pollution or endocrine-disrupting products in food, cannot be easily avoided even by a highly motivated individual. Upstream actions to reduce the production of certain toxic substances might merit further consideration in preterm birth prevention.

Previous efforts at preventing preterm birth have focused on primary, secondary, and tertiary prevention measures.[9] Because there is burgeoning evidence that environmental exposures (ie, social, economic, physical, and chemical) are associated with preterm births, it may now be time to consider a stronger focus on primordial prevention. Primary prevention includes efforts by pregnant women to reduce their individual risk factors while primordial prevention consists of population-level actions and measures that inhibit the emergence and establishment of adverse environmental, economic, and social conditions. One example of primordial prevention of preterm birth is strengthening policies to reduce air pollution because maternal exposure to air pollution is a risk factor for preterm birth. This is a primordial prevention in that it aims to establish cleaner air for all individuals, not just women who are pregnant. A second example of primordial prevention is prohibiting endocrine-disrupting chemicals in food-handling equipment and food contact materials, given that this may be a route of entry of toxic chemicals into the food supply. Primordial prevention often necessitates action by government and industry. In a 2020 study, Shea et al[10] estimated the potential economic costs of avoided preterm births from reduction in anthropogenic particulate matter with a diameter of less than 2.5 μm in the United States to be more than $4.8 billion.[10] They hypothesized that if the number of preterm births attributable to air pollution was reduced by just 1%, this would result in approximately $267 million in benefits.[10]

Because Zhang et al[5] describe novel results, it is too early to assess whether the association they found between phthalate exposure before conception and preterm birth is causal. The study will need to be replicated, especially among couples who are not seeking treatment for infertility. Nonetheless, it may not be premature to begin to implement policies to reduce healthy women's exposures to reproductive toxicants well before they become pregnant.

ARTICLE INFORMATION

Published: April 7, 2020. doi:10.1001/jamanetworkopen.2020.2239

Corresponding Author: Ruth A. Etzel, MD, PhD, Milken Institute School of Public Health, The George Washington University, 950 New Hampshire Ave, NW, Washington, DC 20052 (retzel@gwu.edu).

Author Affiliation: Milken Institute School of Public Health, The George Washington University, Washington, DC.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Chawanpaiboon S, Vogel JP, Moller A-B, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0

2. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*. 2008;371(9608):261-269. doi:10.1016/S0140-6736(08)60136-1

3. Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev*. 2018;11(11):CD012505. doi:10.1002/14651858.CD012505.pub2

4. Institute of Medicine. *Preterm Birth: Causes, Consequences, and Prevention*. National Academies of Science; 2007. Accessed March 2, 2020. http://www.nap.edu/catalog/11622.html

5. Zhang Y, Mustieles V, Yland J, et al. Association of parental preconception exposure to phthalates and phthalate substitutes with preterm birth. *JAMA Netw Open*. 2020;3(4):e202159 doi:10.1001/jamanetworkopen.2020.2159

6. Ferguson KK, McElrath TF, Meeker JD. Environmental phthalate exposure and preterm birth. *JAMA Pediatr*. 2014;168(1):61-67. doi:10.1001/jamapediatrics.2013.3699

7. Gao H, Wang Y-F, Huang K, et al. Prenatal phthalate exposure in relation to gestational age and preterm birth in a prospective cohort study. *Environ Res*. 2019;176:108530. doi:10.1016/j.envres.2019.108530

8. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13(1):43. doi:10.1186/1476-069X-13-43

9. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet*. 2008;371(9607):164-175. doi:10.1016/S0140-6736(08)60108-7

10. Shea E, Perera F, Mills D. Towards a fuller assessment of the economic benefits of reducing air pollution from fossil fuel combustion: per-case monetary estimates for children's health outcomes. *Environ Res*. 2020;182:109019. doi:10.1016/j.envres.2019.109019