It Starts at the Beginning: Effect of Particulate Matter *In Utero*

There is convincing evidence that exposure to ambient air pollution is associated with increased asthma symptoms, exacerbations, and a decline in lung function in children (1–4). Recent studies suggest this relationship may begin *in utero*, when cells are particularly sensitive to the oxidative damage caused by environmental toxins. The timing of exposure during gestation may be crucial in determining specific effects on immune system development and the different stages of fetal lung maturation (5).

Multiple animal studies using murine and primate models have shown that perinatal pollutant exposure results in alteration in distal airways, pulmonary parenchyma, and lung elastic properties with persistent airway hyperresponsiveness (6–8). A nested case control study of 3,482 children with physician-diagnosed asthma from a large birth cohort in British Columbia, Canada, reported that intrauterine exposure to traffic-related pollutants led to a 1.10 (95% confidence interval, 1.05–1.15) odds ratio of pediatric asthma per 10 $\mu g/m^3$ increase in NO_2. The authors caution, however, that they were unable to confidentially distinguish between prenatal and postnatal exposures because of a lack of temporal precision in residential histories (9). This is a common theme in other epidemiologic studies that report a similar correlation (10–13). These studies have been unable to document sensitive time windows of exposure because they have assessed measurements of air pollution with coarse temporal estimates, either averaged over the entire gestational period or inferred from short periods of intensive maternal monitoring.

In this issue of the *Journal*, Hsu and colleagues (pp. 1052–1059) present a well-designed prospective cohort study of 736 full-term children born in Boston, Massachusetts, to assess whether *in utero* exposure to ambient air pollution is associated with the development of asthma (14). In contrast to other studies, the authors were able to address the effect of exposure timing by estimating weekly maternal levels of particulate matter with diameter $\leqslant 2.5$ μg ($PM_{2.5}$), a major component of traffic-related air pollution, throughout gestation. For exposure assessment, they used a well-validated satellite-based model with land use regression and spatial temporal resolution. Their final statistical models adjusted for a number of potential confounders, including measurements of socioeconomic status, allergen exposures, and household crowding.

The study found that increased levels of $PM_{2.5}$ during midgestation (16–25 wk) was associated with the development of asthma. These weeks correspond to the late pseudoglandular and canalicular phases of lung development, when the airways are developing, airway epithelium forms, and type I pneumocytes differentiate. During this time in embryogenesis, the airway epithelium starts to secrete immune modulators such as IL-25 and IL-33, which may enhance susceptibility to asthma. Interestingly, in sex-stratified analyses, the association the authors found was limited to boys. The authors postulate that this may be caused by sex-specific differences in lung development, with males exhibiting later fetal breathing and surfactant production. This finding gives the reader pause, however, given that no effect was noted in females at an earlier time during prenatal exposure.

Although the overall increased risk for asthma reported was small on an individual basis, the results are compelling because of the careful design and execution of the study. The authors increased their power of detecting a difference by selecting a population of children at higher risk of developing asthma. They also did an excellent job capturing the predictor of interest, exposure to $PM_{2.5}$, and outcome, maternal-reported, clinician-diagnosed asthma. They enrolled a prospective cohort of pregnant women and prospectively captured the outcome of interest in the children, assessed at 3-month intervals via telephone interviews and face-to-face meetings for the first 24 months, then annually thereafter until the children were 6 years of age. A detailed list of important clinical variables were collected including household crowding and family stress, measured with the Crisis in Family Systems-Revised survey, administered prenatally (15). They formally captured evidence of maternal atopy, using self-reported doctor-diagnosed asthma, eczema, and/or hay fever and infant birth weight and gestational age z score. Smoking status of the mother and others in the household was also prospectively evaluated prepartum and at each postnatal study visit.

Although the findings of this article provide novel insights into sensitive windows of *in utero* pollutant exposure with intriguing mechanistic postulations on the development of asthma, care should be taken in the interpretation of these results. The study has the same intrinsic limitation of all observational studies, with misclassification of exposures and outcomes, residual confounding, and an inability to infer causation. For example, $PM_{2.5}$ levels do not account for indoor exposures, clinician-diagnosed asthma is by maternal report only, and smoking, an important confounder, has a low prevalence in the population. There is particular concern for ecologic fallacy inherent to a multilevel study, in which the asthma cases are clustered into small communities whose

C.H.G. receives funding from the Cystic Fibrosis Foundation, the National Institutes of Health (R01HL103965, R01HL113382, R01AI101307, U M1HL119073, P30DK089507), and the U.S. Food and Drug Administration (R01FD003704). C.S. receives funding from the National Heart, Lung, and Blood Institute T32HL007287 and National Institutes of Health/National Institute of Environmental Health Sciences P30ES007033.

Am J Respir Crit Care Med Vol 192, Iss 9, pp 1025–1035, Nov 1, 2015
Internet address: www.atsjournals.org

composition is significantly different from that of the general population. Most of the enrolled mothers were minorities, with 66% having less than a 12th grade level education and a high proportion earning less than $20,000/yr. Although the authors have put concerted effort into adjusting for these characteristics, there is still concern that pollution levels track with some unmeasured variable that may be responsible for the increased incidence of asthma. One means of unraveling such potential confounding is to restrict the analysis to those with higher socioeconomic status to see whether the trend persists. Such an analysis will lower the power to detect a change but may reinforce the findings in the adjusted analysis (16).

Although Hsu and colleagues used sophisticated models of pollution exposure with fine temporal resolution, postnatal exposure to air pollution correlates strongly with prenatal levels, and it may be difficult to disentangle these interrelated effects. Controlled exposure studies in mice have found that although pre and postnatal $PM_{2.5}$ exposure leads to significant alteration of alveolar structure and lung elastic properties, prenatal exposure alone did not alter lung function (6). These data appear to conflict with the findings of the study by Hsu. In animal studies, one can exactly control the timing and exposure, whereas in human observations, we can merely try to capture as best as possible both the timing and dose of exposure. In contrast to animal exposure studies, humans are born into the same environment as they develop, and they will continue to be exposed to similar pollutants.

Overall, this study adds significantly to the body of literature that documents the adverse effects of these early gestational exposures. When trying to weigh the strengths of associations noted in observational studies, one should evaluate the presence of biologic plausibility, size of the effect (the larger the effect, the more likely it could represent a true association), temporal relationship (the risk factor was determined prior to the determination of the outcome), and the relation to other existing literature. In this case, the authors present a compelling biologic model, appropriate temporal association, and supporting existing literature (17). These data support the potential to mitigate against harmful exposures *in utero* by knowing the time at which the fetus may be at highest risk. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Coralynn Sack, M.D.
Department of Medicine
University of Washington School of Medicine
Seattle, Washington

Christopher H. Goss, M.D., M.Sc.
Department of Medicine
University of Washington School of Medicine
Seattle, Washington
Department of Pediatrics
University of Washington
Seattle, Washington
and
Seattle Children's Research Institute
Seattle, Washington

References

1. Gent JF, Koutrakis P, Belanger K, Triche E, Holford TR, Bracken MB, Leaderer BP. Symptoms and medication use in children with asthma and traffic-related sources of fine particle pollution. *Environ Health Perspect* 2009;117:1168–1174.
2. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014; 383:1581–1592.
3. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, Evans R III, Gruchalla R, Morgan W, Stout J, *et al*. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008;121: 1133–1139.
4. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, *et al*. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057–1067.
5. Pinkerton KE, Joad JP. Influence of air pollution on respiratory health during perinatal development. *Clin Exp Pharmacol Physiol* 2006;33: 269–272.
6. Mauad T, Rivero DH, de Oliveira RC, Lichtenfels AJ, Guimarães ET, de Andre PA, Kasahara DI, Bueno HM, Saldiva PH. Chronic exposure to ambient levels of urban particles affects mouse lung development. *Am J Respir Crit Care Med* 2008;178:721–728.
7. Fanucchi MV, Plopper CG, Evans MJ, Hyde DM, Van Winkle LS, Gershwin LJ, Schelegle ES. Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. *Am J Physiol Lung Cell Mol Physiol* 2006;291:L644–L650.
8. Manners S, Alam R, Schwartz DA, Gorska MM. A mouse model links asthma susceptibility to prenatal exposure to diesel exhaust. *J Allergy Clin Immunol* 2014;134:63–72.
9. Clark NA, Demers PA, Karr CJ, Koehoorn M, Lencar C, Tamburic L, Brauer M. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010;118: 284–290.
10. Jędrychowski WA, Maugeri U, Spengler J, Mróz E, Flak E, Klimaszewska-Rembiasz M, Jacek R, Sowa A. Dose-dependent relationship between prenatal exposure to fine particulates and exhaled carbon monoxide in non-asthmatic children: a population-based birth cohort study. *Int J Occup Med Environ Health* 2013;26: 73–82.
11. Mortimer K, Neugebauer R, Lurmann F, Alcorn S, Balmes J, Tager I. Air pollution and pulmonary function in asthmatic children: effects of prenatal and lifetime exposures. *Epidemiology* 2008;19:550–557.
12. Gaffin JM, Kanchongkittiphon W, Phipatanakul W. Perinatal and early childhood environmental factors influencing allergic asthma immunopathogenesis. *Int Immunopharmacol* 2014;22: 21–30.
13. Rosa MJ, Jung KH, Perzanowski MS, Kelvin EA, Darling KW, Camann DE, Chillrud SN, Whyatt RM, Kinney PL, Perera FP, *et al*. Prenatal exposure to polycyclic aromatic hydrocarbons, environmental tobacco smoke and asthma. *Respir Med* 2011;105: 869–876.
14. Hsu H-HL, Chiu Y-HM, Coull BA, Kloog I, Schwartz J, Lee A, Wright RO, Wright RJ. Prenatal particulate air pollution and asthma onset in urban children: identifying sensitive windows and sex differences. *Am J Respir Crit Care Med* 2015;192:1052–1059.
15. Berry C, Shalowitz M, Quinn K, Wolf R. Validation of the Crisis in Family Systems-Revised, a contemporary measure of life stressors. *Psychol Rep* 2001;88:713–724.
16. Greenland S. Ecologic versus individual-level sources of bias in ecologic estimates of contextual health effects. *Int J Epidemiol* 2001; 30:1343–1350.
17. Noel Weiss TK. Epidemiologic methods. New York: Oxford University Press; 2014.