

Maternal Medications in Pregnancy and Childhood Asthma: Causation or Association?

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The unexpected increase in the prevalence of asthma in all age groups in the last 2 decades of the 20th century has been a major concern for parents and health care providers. It has also presented a challenge for asthma researchers but also an opportunity. There must be reasons that the incidence of asthma has increased, and finding causes of the asthma “epidemic” would lead to improved understanding of the pathogenesis of asthma and, more importantly, clues for developing strategies for treatment and prevention. Leading hypotheses at present involve an imbalance in the immune response, possibly related to improved hygiene or a change in the microbiome. In either case, confirmation remains far off, and strategies for asthma management leading from these hypotheses would be unclear. It is, of course, probable that more than 1 mechanism is responsible. Among other potential mechanisms is the hypothesis that children exposed in utero to 1 or more of a variety of drugs or toxins might be more likely to develop asthma. The association of childhood asthma with maternal cigarette smoking in pregnancy demonstrates that such an effect is within reason.¹ There have certainly been systematic changes in medications or toxins to which fetuses are exposed in phase with the asthma epidemic. Proving that exposure in utero to 1 or more pharmaceuticals contributes to the pathogenesis of asthma would lead to clear strategies for prevention.

One in utero exposure that has been associated in epidemiologic studies with subsequent childhood asthma is to proton pump inhibitors (PPIs) and/or histamine H_2 receptor (H_2) antagonists (H_2 Bs). In this issue of the journal, Yitshak-Sade and colleagues report a careful epidemiologic investigation of maternal use of medications to modify gastric acidity during pregnancy and the presence of asthma in offspring. They developed reliable data on drug use in pregnancy and the diagnosis of childhood asthma for a majority of the children born in a relatively large population in southern Israel, the type of data that are not easily available in many parts of the United States. Their analysis illuminates this issue; in their population, although an association between exposure in utero and asthma at 2 years of age was identified,

the relative risk was smaller than that previously reported. More importantly, they present persuasive evidence that the association represents, at least in part, confounding rather than causation.

An association between 2 observations that might represent confounding rather than causation is a major challenge for epidemiologic studies that can never be completely eliminated. Explanations for the weak association (RR, 1.09) in this study between prenatal H_2 B/PPI exposure and childhood asthma could be that women prone to esophageal reflux during pregnancy are more likely to have children with asthma regardless of medications taken during pregnancy or that children with a tendency toward asthma are more likely to be symptomatic if they also have esophageal reflux because they inherited a tendency toward reflux from their mothers. The authors support the possibility of confounding by identifying an association between maternal use of acid suppressive therapy 2 years after delivery and childhood asthma (RR, 1.29) for a subset of women who had not used such therapy during pregnancy.

It is interesting to compare these findings on the possible effect of prenatal exposure to acid-modifying agents with the controversy regarding fetal exposure to acetaminophen and childhood asthma. Although population-based studies of prenatal acetaminophen use and childhood asthma have produced conflicting results,^{2–4} there is considerable epidemiologic evidence of a clinically important relative risk for childhood asthma in children exposed in pregnancy to acetaminophen. From a public health point of view, many more fetuses are likely to be exposed to acetaminophen than to acid-modifying

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agents. Furthermore, the possibility of confounding seems somewhat less theoretically likely with acetaminophen than in the case of acid-modifying agents, as acetaminophen is taken for a wider variety of indications. An argument against confounding in the case of acetaminophen exposure is also supported by the observation of an interaction between acetaminophen exposure during pregnancy and the presence of a glutathione S transferase Pi (*GSTP1*) gene in the mother.⁵

For fetal exposures to both acid-modifying agents and acetaminophen, it seems unlikely that further epidemiologic studies will definitively establish causation. In neither case would future studies be able to completely eliminate the possibility of confounding. It will likewise be difficult in either case for such studies to completely eliminate the possibility of causation. Causation will only be definitively tested by prospective controlled trials. Such trials would require a large number of subjects and would be particularly challenging because the subjects are pregnant. Considering the uncertainties of the observational evidence implicating prenatal H2B/PPI use and childhood asthma, the relatively modest association, and the logistical difficulties of conducting a long-term trial, randomized clinical trials for prenatal exposure to acid-modifying agents may not be a high priority at present. By comparison, the higher relative risk, the greater number of children impacted, and the somewhat lower likelihood of confounding increase the relative priority for studying

the association of fetal exposure to acetaminophen and childhood asthma. Although epidemiologic studies may not be able to establish or eliminate the possibility of causation, careful studies such as the work of Yitshak-Sade and colleagues are essential to setting priorities and the development of rational strategies to settle the important issue of whether exposures during pregnancy contribute to the worldwide challenge of childhood asthma.

Declaration of Conflicting Interests

The authors have no relevant financial relationships or conflicts of interest to disclose.

Reference

1. Vieira SE. The health burden of pollution: the impact of prenatal exposure to air pollutants. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1111–1121.
2. Cheelo M, Lodge CJ, Dharmage SC, et al. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. *Arch Dis Child*. 2015;100(1):81–89.
3. Sordillo JE, Scirica CV, Rifas-Shiman SL, et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. *J Allergy Clin Immunol*. 2015;135(2):441–448.
4. Källén B, Finnström O, Nygren KG, Otterblad Olausson P. Maternal drug use during pregnancy and asthma risk among children. *Pediatr Allergy Immunol*. 2013;24(1):28–32.
5. Perzanowski MS, Miller RL, Tang D, et al. Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban low-income cohort. *Thorax*. 2010;65(2):118–123.