

Maternal antibiotic use and childhood asthma: the missing link?



Most childhood asthma begins very early in life in the form of recurrent respiratory illnesses and wheezing in response to infections (usually viral) in the first year of life. Half of all cases of asthma are diagnosed by 6 years of age. This situation has led investigators to focus research efforts on pregnancy and pregnancy-related factors that might be important in early-life asthma onset. Several factors are under investigation, one of which is maternal antibiotic use.

In *The Lancet Respiratory Medicine*, Jakob Stokholm and colleagues report that maternal antibiotic use for any type of infection increases the risk of incident asthma in the offspring, independent of timing of antibiotic use relative to pregnancy and a wide range of other potential confounding variables.¹ The increase in risk was modest—about 20%—but was consistent across the pre-pregnancy, pregnancy, and post-partum periods for 80 weeks before and after the pregnancy. The infections in the mothers were ones that occur frequently in relatively healthy women of child-bearing age; most were respiratory tract infections (68%), in addition to urinary tract infections (30%) and other infections (14%). This study has no obvious methodological problems, and the data were obtained from a large national registry of Danish pregnancies and births over a 14-year period (1997–2010), and almost 1 million children were included in the analysis. Other investigators have also reported this association between maternal antibiotic use and childhood asthma.²

Stokholm and colleagues' paper reports good news for clinicians. No reason exists to deny pregnant women antibiotics for the treatment of a clear-cut bacterial respiratory or urinary tract infection because of perceived future asthma risk in the child. The clear and present danger of a bacterial infection takes precedence over a modest increase in risk of future asthma, and this paper suggests that maternal antibiotic use and childhood asthma are linked by some as-yet unidentified third, or mediating, factor, instead of being directly linked.

The associations reported in this study suggest the possibility of an unmeasured factor—or factors—present in both the mother and the child, which confer

both an increased risk of infection in the mother and of asthma in the child. Several possibilities exist. One factor noted by the authors is the microbiome. However, since Stokholm and colleagues discuss the microbiome extensively, we refer readers to the paper for more about this topic. A second possibility is genetic susceptibility, although the genes conferring risk of infection in the mother and asthma in the child have yet to be defined. In our opinion, the most likely factor that could help explain infection risk in the mother and asthma development in her child is a nutritional deficiency, most probably vitamin D.³ Vitamin D deficiency is prevalent in young women of childbearing age, with around 70% having amounts lower than 30 ng/mL, which is the minimum for normal immune system function.⁴ Cord blood provides a direct link between mother and child. Evidence from one study suggests that increased levels of 25-hydroxy-vitamin D3 in the cord blood led to reduced respiratory infections in the newborn and a lower asthma risk, but this study was too underpowered to be definitive.⁵ Although vitamin D deficiency has been studied as a risk factor for respiratory infections in adults, the results have been inconclusive, partly because controlled trials have used inappropriate dosing schedules to address this question.⁶

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The microbiome, genetic susceptibility, and vitamin D deficiency probably all contribute to the associations described by Stokholm and coworkers. Additionally, a range of other nutrients that affect immune function (eg, retinoic acid, folic acid, vitamin C, vitamin E, and N-3 fatty acids) could either interact with vitamin D or independently contribute to the associations with antibiotic use in the mother and asthma in the child. These other nutrients may also be worthy of study.^{7,8} Further research into all these factors and their association with the risk of infection, asthma, and other autoimmune diseases, is clearly needed.

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