clinical markers that could be used to diagnose these specific asthma phenotypes in early life. We are therefore still far from applying big data in a personalized way, to improve asthma diagnosis and to provide avenues for prevention of this prevalent, childhood disease. ■

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Asthma and Prenatal Inflammation

The asthma syndrome comprises various forms, which respond differently to noxious influences during subsequent vulnerable time windows. Some forms of asthma are more or less genetically determined, whereas others are susceptible to exposures encountered in early childhood, such as viral infections and sensitization to food or inhalant allergens (1). Although these latter factors require some time of exposure over the first postnatal years, already the growing fetus may be affected by maternal exposures and conditions during pregnancy, which is illustrated by the effect of in utero smoke exposure on subsequent lung function (1).

These prenatal effects highlight the role of the interface between mother and child; that is, the placenta. Beyond hormone production and exchange of nutrients, metabolites, and gases, the placenta has to maintain tolerance between two mismatched human leukocyte antigen systems.

These complex functions require undisturbed placentation, and any interference with this process such as oxidative stress or hypoxia may derange the homeostasis of metabolism and immunity (2). The quality of placentation thus determines the fate of the pregnancy, ranging continuously from normal development over preeclampsia and fetal growth impairment to miscarriage (3). Preeclampsia is an inflammatory status leading to endothelial damage, which in advanced stages manifests clinically with the characteristic triad of symptoms: hypertension, proteinuria, and edema.

But what are the mechanisms behind preeclampsia? Beyond oxidative stress and serious hypoxia, preeclampsia has consistently been associated with reduced numbers of regulatory T cells (4), which in normal pregnancies keep proinflammatory Th17 cells at bay (5). These are the same key players as in other inflammatory conditions such as allergy and asthma. The question now arises of whether a prenatal inflammatory status can persist and pave the way to future chronic inflammation.

In this issue of the *Journal*, Stokholm and colleagues (pp. 614–621) exactly address the question whether preeclampsia predisposed children to inflammatory disease manifesting at school age (6). Their main findings are strong associations of preeclampsia with sensitization to inhalant and food allergens, allergic rhinitis, treatment with inhaled corticosteroids for asthma (odds ratio = 4.01; 95% confidence interval, 1.11–14.43]), and bronchial hyperresponsiveness in 7-year-old children of the $COPSAC_{2000}$ (Copenhagen Prospective Studies on Asthma in $Childhood_{2000}$) birth cohort, who are all born to mothers with asthma. As this population is rather selected, Stokholm and colleagues complemented their findings with data from Danish nationwide registries, which offer the advantage of a largely unbiased population at the cost of lower data quality compared with the meticulously assessed participants of $COPSAC_{2000}$. The registry data replicated most associations, although at much lower effect sizes. Interestingly, the effect sizes were stronger for longer duration of preeclampsia. Although residual confounding can never be fully excluded in observational studies, the consistency over two different study types and dose relationship with duration argue in favor a true effect.

In the registry, preeclampsia was also associated with maternal asthma, as already suggested by a comparably high incidence of preeclampsia in the mothers with asthma of $COPSAC_{2000}$. Thus, it is tempting to speculate that asthma is partially "inherited" through prenatal inflammation.

But why should a rare condition such as preeclampsia be relevant for the development of a rather common disease? For childhood asthma, the population-attributable risk fraction of preeclampsia is below 1%, according to Stokholm and colleagues. However, clinically manifest preeclampsia, particularly with a longer duration, might just be the tip of the iceberg of intrauterine inflammation. We may anticipate many more pregnant women with low-grade inflammation not presenting with the obvious symptoms of the advanced stages, and thus not being detected in routine checkups, let alone reported to registries and studies. Conversely, the effects of preeclampsia with shorter duration were hardly detectable, thereby suggesting that the clinical symptoms of preeclampsia are inadequate markers of the relevant underlying inflammatory processes. Thus, future studies may assess low-grade inflammation, hypoxia, and oxidative stress throughout pregnancy more specifically by the relevant prostaglandin isomers (2), distinct cytokine patterns (7), or noncoding RNAs (8).

The fetal response to prenatal inflammation is intrauterine growth restriction reflected by the well-known association of asthma and low birth weight (9). If inflammation aggravates, preeclampsia may progress to eclampsia, which presents with convulsions and multiorgan failure and threatens the lives of both mother and child. To prevent this serious condition, induction of labor or emergency cesarian section is often indicated. Thus, preeclampsia may act as a confounder by indication in the association of cesarean section and asthma, which has previously been attributed to inadequate microbial exposure when bypassing the birth canal by cesarean section. Stokholm and colleagues are well familiar with this idea (10) and also adjusted the present analyses for cesarean section: They observed a high section rate in preeclamptic mothers, but hardly a change in the reported estimates, thereby suggesting a genuine effect by preeclampsia on asthma.

If microbial contamination during vaginal birth or its absence does not explain the effect of preeclampsia, still ascending infections might contribute to preeclampsia or premature birth (e.g., by induction of reactive oxygen species) (2). Microorganisms are potent elicitors of inflammatory responses anyway, and subclinical infection may also trigger systemic inflammation. This has been suggested for the effects

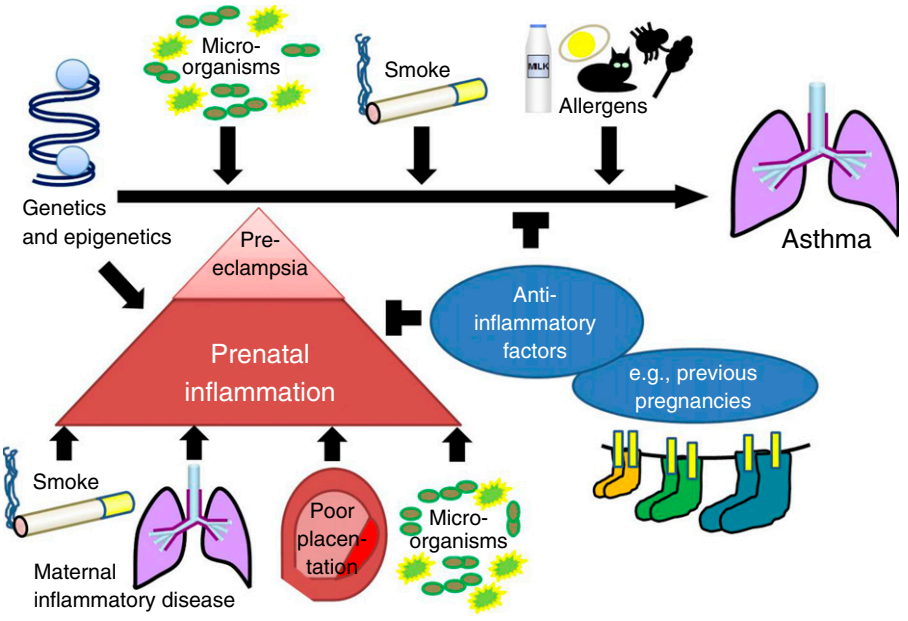

Figure 1. Synopsis of prenatal inflammation and other determinants of asthma.

of periodontal disease on preeclampsia mediated by dissemination of gram-negative bacteria and secretion of proinflammatory cytokines (11), although reverse causation or a common inflammatory etiology also are discussed (12). In addition, maternal inflammatory bowel disease, which is associated with a skewed gut microbiome, has been reported as a risk factor for severe preeclampsia, particularly in severe cases requiring oral corticosteroid therapy (13).

The risk for preeclampsia decreases over subsequent pregnancies, as verified by Stokholm and colleagues (6). This is an intriguing parallel to the birth order effect of the hygiene hypothesis (14). Birth order has often been interpreted as number of (older) siblings, and thus as risk for infection by "unhygienic contact" (14). In the light of the present findings, however, the birth order effect might point toward an antiinflammatory effect of previous pregnancies (2, 5), and that in a dose-dependent manner.

Obviously, not all forms of asthma are likely to be induced by prenatal inflammation (1), and prenatal inflammation does not necessarily lead to subsequent asthma, as detrimental effects of prenatal inflammation might be overruled by antiinflammatory factors (Figure 1). Indeed, there is evidence for antiinflammatory effects by favorable environmental exposures pre- (15) and postnatally (16, 17). Hence, the article by Stokholm and colleagues will definitively stimulate further research into prenatal inflammation and to those of its determinants that are amenable to modification (6). ■

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Maintaining the Benefits of Pulmonary Rehabilitation
The Holy Grail

Pulmonary rehabilitation (PR) confers benefits across multiple outcome areas for patients with chronic obstructive pulmonary disease (COPD) (1). It is a high-value multidisciplinary treatment (2) that is tailored to the needs of the individual patient according to the type of underlying disease, medical comorbidities, symptoms, exercise tolerance, functional disability, and goals; indeed, PR is true "personalized medicine" (3). The benefits of PR do wane over time, however (4), which has led to interest in strategies to maintain the gains achieved. To date, the effects of exercise-based maintenance programs after PR have been variable (5); thus, their role remains controversial.