

Prenatal factors and the development of asthma

Rajesh Kumar

Division of Allergy and Immunology, Children's Memorial Hospital, Chicago, Illinois, USA

Correspondence to Rajesh Kumar, MD, Children's Memorial Hospital, 2300 Children's Plaza, Box #60, Chicago, IL 60614, USA
Tel: +1 773 327 3710; fax: +1 773 327 3790;
e-mail: rkumar@childrensmemorial.org

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Purpose of review

There is increasing evidence that both prenatal and perinatal events influence both allergic diseases and early-life respiratory morbidity.

Recent findings

Studies in the last year have suggested that in-utero exposures including tobacco smoke exposure, dietary exposures including vitamin D, and prenatal infection and exposure to microbial products may modulate both atopy and respiratory disease. There have been studies revealing gene $\times$ environment interactions between inflammatory pathway genes and in-utero smoke exposure. There have also been studies which have revealed that prenatal exposure to endotoxin may be protective. On the other hand, a recent study also suggested that chorioamnionitis may increase the risk of recurrent wheezing in combination with preterm birth. Finally, two separate large cohort studies evaluated maternal diet in pregnancy and suggested that vitamin D levels may be protective against asthma and wheezing.

Summary

There is epidemiological evidence for multiple prenatal factors impacting early-life respiratory morbidity. The mechanisms of these factors need further investigation and may act via various pathways which include effects on lung development, allergic and nonallergic inflammation, and airway remodeling. It remains to be determined if some of these early-life factors which predispose to wheezing will all translate into increased risk of asthma.

Keywords

asthma, diet, environmental tobacco smoke, infection, in-utero environment, stress

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Introduction

Although traditional perinatal and postnatal 'hygiene hypothesis' risk factors play a clear role in the development of asthma and atopic disease, there has been emerging interest in the prenatal determinants of respiratory disease. Recent studies have revealed evidence of airway remodeling in the first years of life [1•] and longitudinal studies have suggested that children with reduced lung function in early life are at higher risk of asthma if they develop atopy [2]. Thus, similar to the barker hypothesis for cardiovascular disease [3], there may be in-utero and early-life factors which play a role in airway development, inflammation, and remodeling. It is possible that these factors may act in concert with postnatal atopy-promoting factors to predispose to wheezing and asthma.

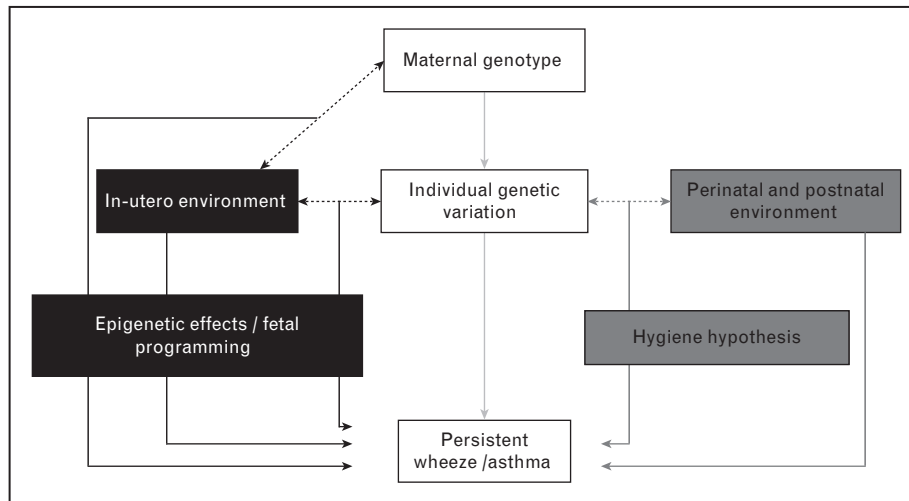
The above-mentioned concept is illustrated in Fig. 1. Specifically, although there are traditional postnatal and perinatal factors which are well established to be associated with asthma, there may also be prenatal factors which also lead to this phenotype by different mecha-

nisms. This may be because of direct effects of exposures on the developing lung and immune system, gene–environment interactions between the fetus and the in-utero environment, interactions between maternal genotype and the relevant exposure which modify the in-utero environment, and finally epigenetic effects.

The review will seek to place in context recent studies which evaluate the role of the in-utero environment on asthma development. This will include in-utero tobacco smoke exposure, in-utero exposure to immunomodulatory microbial products, maternal diet, infection and chorioamnionitis, and stress.

In-utero exposures to tobacco smoke

The overall rate of smoking in women aged 18–44 years was 23–25% in the US DHHS 2002 survey. This is even more prevalent in low-income women, of whom 27% were smokers. With respect to asthma and respiratory morbidity, in-utero exposure to environmental tobacco smoke (ETS) impairs lung function [4–8] and increases bronchial hyperreactivity [9,10]. This may be the underlying mechanism of the very well documented association

Figure 1 Hypothesized interrelationships of prenatal and postnatal factors on the development of recurrent wheezing and asthma

Black lines indicate prenatal pathways of effects on persistent wheezing and asthma. The dark grey lines represent postnatal and perinatal factors associated with asthma via immunomodulatory (hygiene hypothesis) and other pathways. Dotted lines represent interactions.

between maternal smoking during pregnancy and asthma [6,11–16]. Finally, maternal smoking results in higher neonatal Th2 cytokine responses to antigen, decreased production of interferon gamma to mitogen [17], and impaired Toll-like receptor (TLR)-mediated responses [18]. It is likely that in-utero smoking has effects on asthma incidence and respiratory morbidity in children by a combination of changes in lung growth, airway responsiveness, and impaired adaptive and immune response to viral pathogens.

It is difficult to separate the effect of prenatal ETS exposure from the effect of postnatal ETS exposure because women who smoked during pregnancy are likely to continue smoking after delivery. Still, there is some evidence to suggest that the association between in-utero exposure to maternal smoking with wheeze and/or asthma in children is greater than that of postnatal exposure [4,12,14,15,19,20*].

The effects of exposure in adolescence and beyond are more difficult to establish. One study revealed that there was a persistent risk in adolescent girls [11], whereas other prior studies only showed a persistent effect in adolescent boys [21]. Other studies have revealed a waning importance of in-utero exposure in the third decade of life as compared with the participants themselves smoking [22,23]. This decreasing effect over time may imply that some of the effect is because of early effects of exposure on the developing lung.

The suggestion that the effects are due in part to developmental and inflammatory remodeling effects of tobacco smoke exposure is supported by recent genetic

studies. The effect of smoke exposure *in utero* on asthma is modified by genetic polymorphisms in nicotine-metabolizing genes such as glutathione S-transferase (GST) [24,25]. Findings that maternal genotype of this metabolizing enzyme affect airway hyperreactivity independent of fetal genotype [9] imply that the toxic metabolites may have a direct effect on inflammation and neonatal lung development.

The role for inflammatory and remodeling pathways in this process is reinforced by findings implicating TGF-beta and IL-1R polymorphisms. One study revealed that, if children with a TGF-beta functional promoter polymorphism were exposed to tobacco smoke *in utero*, they were at higher risk of asthma [26*]. Another study by Ramadas *et al.* [27] evaluated 921 children in an unselected subset of the Isle of Wight birth cohort who had been followed to 10 years of age and found that, in children exposed to in-utero cigarette smoke, a polymorphism in the IL-1R gene was associated with a 4.5-fold increased risk of childhood asthma diagnosis. Also, recent animal data revealed that nicotine enhances lung branching morphogenesis, which may result in changes in the number and size of conducting airways [28]. Thus there may be both developmental and inflammatory/remodeling pathways which predispose susceptible individuals to respiratory disease after in-utero smoke exposure.

Whether there are also immunological or epigenetic changes associated with smoking which may predispose to asthma remains unclear. The possibility of ongoing molecular epigenetic processes has been suggested by one study demonstrating a multigenerational and

presumably epigenetic effect of in-utero smoking with asthma in the grandchildren [29]. Contrary to a recent smaller study [30], a large study of 9000 children revealed an association of prenatal exposure to ETS and aeroallergen sensitization. This was greater than the effect seen with postnatal exposure [31•].

Finally, some recent animal and in-vitro studies would suggest that exposure to tobacco smoke may modify immunological processes as well. A recent mouse model of smoke exposure *in utero* revealed that exposure to ETS *in utero* was associated with an increased rate of sensitization to allergen [32]. Although ETS is associated with altered TLR responses in cord blood, it is not clear whether this is persistent or affects the development of sensitization [18]. Thus, it seems that ETS affects lung function and hyperresponsiveness, but the immunological effects on atopic predisposition remain unclear.

In-utero exposure to immunomodulatory microbial products

It has been found that a number of the epidemiological effects of 'hygiene hypothesis' protective factors are due to the effects of endotoxin and other microbial exposure [33,34] via the innate immune system [35]. Interestingly, the investigators from the PARSIFAL study previously found that prenatal exposure to farming environments was associated with increased expression of innate immune receptors (TLR2, TLR4, and CD14) and with decreased incidence of atopic sensitization [36•]. A recent follow-up publication from this found that in-utero exposure to farming environments in combination had the protective effects on asthma phenotypes, and that the prenatal exposure may be even more important than early-life exposures [37]. Thus, even some of the immunomodulatory exposures which have been shown to be important in early postnatal life may have their effects start in prenatal life.

Maternal diet in pregnancy and antioxidants

There have been a number of studies of maternal diet in pregnancy and asthma and wheezing. These studies have focused on vitamin E and antioxidants, vitamin D and long-chain polyunsaturated fatty acids. There are two groups which have found that vitamin E in pregnancy was protective, decreasing the incidence of asthma and wheezing [38–40]. In one cohort, follow-up was continued to age 5, whereas the other cohort has followed these children only till 2 years of age at the time of the study. Also, all of these studies except for one [39] were based on maternal food frequency questionnaires. In the study by Devereux *et al.* [39], high maternal alpha tocopherol levels at 12 weeks' gestation were correlated with less atopic sensitization and increased post-bronchodilator FEV1 in a subgroup. Because these results contrast with prior equivocal intervention trials [41], these findings may

suggest that the effect of vitamin E occurs at an early stage of development, as has been suggested by others [42].

Similar findings have been noted for other antioxidant compounds including selenium in cord blood [43,44]. In the SEATON cohort, both cord blood and maternal plasma selenium were measured. Although the study found a protective effect of selenium levels on early wheezing, like the earlier study by Shaheen *et al.* [44], this effect was no longer present by 5 years of age. This brings up the question of whether deficiencies in antioxidants result in a developmental or remodeling effect which is less important as children grow.

Vitamin D levels have been theorized to be associated with asthma as well, with two larger studies suggesting a negative correlation of maternal intake with recurrent wheezing [45•,46•]. This is in contrast to a recent study of a smaller number of infants (178 with asthma) which revealed a positive association with asthma and maternal vitamin D levels [47]. Larger studies with direct measurement of levels in pregnancy and cord blood are needed to resolve the issue.

Finally, there have been a few studies of diet which evaluated prenatal exposure to higher levels of n-3 long-chain polyunsaturated fatty acids and lower levels of n-6 LCPUFA. There are a number of mechanisms whereby n-3 LCPUFA may decrease inflammation, as has been recently reviewed [48], including decreased neonatal lipid peroxidation, altered antigen-presenting cell and neutrophil function, reduced production of leukotriene B4, and T-cell regulation. Contrary to two studies of smaller size which evaluated cord blood fatty acid profiles and early childhood disease [49,50], a larger cohort study found that LCPUFA was not associated with wheezing in childhood [51]. In contrast, another recent large dietary study of asthma at 5 years of age in a cohort of 1253 children [52] confirmed previous findings [53–55] that higher maternal intake of fish was protective. This effect has been hypothesized to be because of fatty acid profiles in the diet. As such, the role of fatty acids in maternal diet in the development of asthma remains unresolved at this time.

Preterm birth, low birth weight, and chorioamnionitis

There are multiple positive associations for asthma and prematurity [56–60], including a recent meta-analysis of 19 studies [57]. This association is not likely to be related to atopy. There have been a number of studies which suggested either no association [61] or decreased risk of atopic disease [56,62,63]. However, this association is not universal across studies and a major limitation of previous studies is that they did not consider the underlying pathogenesis of preterm birth.

Not accounting for the effect of chorioamnionitis, a major pathway for preterm birth, may also have led to some discrepant findings on the role of prematurity in asthma pathogenesis [64,65]. Chorioamnionitis, a major cause of preterm birth [66–68], also has been associated with markers of neonatal airway inflammation and remodeling [69,70]. In this regard, febrile episodes in pregnancy (especially the third trimester) have been associated with later development of asthma in the offspring [71,72].

Prior studies of the effects of chorioamnionitis [72,73] revealed a relatively modest risk of asthma in comparison with a study by Kumar *et al.* [74[•]] which evaluated the joint effect of prematurity and chorioamnionitis. This study found that chorioamnionitis and prematurity had a joint effect of increasing the risk of recurrent early childhood wheezing in an inner city population [74[•]].

Maternal stress during pregnancy

Maternal stress during pregnancy has been hypothesized to be a factor in the development of asthma and allergic disease. In animal studies, increased maternal stress in the prenatal period is associated with an elevated cortisol response to stress in the newborn that affects Th1/Th2 differentiation [75]. A study in humans found that higher caregiver stress during the first 6 months after birth was associated with greater allergen-specific proliferation response, higher total IgE levels, increased production of TNF- α , and decreased INF- γ [76]. In a prospective birth cohort study by the same group, prenatal stress was a predictor of wheezing in infancy [77].

It is hypothesized that chronic stress may lead to hypo-responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis with a reduction of cortisol secretion and increased secretion of inflammatory cytokines usually counter-regulated by cortisol [78]. In a study of 89 pregnant mothers in an inner city environment, salivary cortisol was collected five times a day over 3 days and correlated with total IgE, revealing that those with a flattened diurnal cortisol slope had higher maternal IgE levels [78]. This may be important because parental IgE levels have been associated with those of the offspring [79,80]. Interestingly, a recent article highlights the possibility that these prenatal exposures may act in concert. A study of stress and diesel particulate exposure *in utero* revealed that there was a significantly increased risk when the combination of these exposures was considered [81].

Other factors

There have been other studies which have found associations of asthma with medication such as paracetamol [82], as well as with the combination of in-utero exposures to pollutants and ETS [83].

Conclusion

Thus many studies would suggest that prenatal factors including smoking, diet, infection, and exposure to immunomodulatory agents may impact respiratory health in early life. It remains to be determined whether these associations with wheezing equate to increased risk of asthma in long-term follow-up studies. For those factors associated with respiratory morbidity, it will be important to determine if these effects are due to remodeling and developmental changes or epigenetic changes. Furthermore, evaluation of the additive and joint effects of these multiple-related risk factors will be important to determine which individuals are at significantly increased risk of respiratory morbidity as a result of prenatal factors.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 753–754).

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