

Fetal Programming: Early-life Modulations that Affect Adult Outcomes

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Abstract Asthma is a common disease, and the number of people diagnosed with it increases every year. Although genetic background and environmental exposures play major roles in the development of asthma, one cannot overlook the developmental origin of adult disease or fetal programming theory. This review examines the social, genetic, and environmental factors that are associated with fetal programming of asthma. We also present recent studies from our laboratory that strengthen these observations. It is our hope that the reader will come away with a current view of fetal programming in asthma.

Keywords Asthma · Fetal programming · Offspring · Epigenetics

Introduction

Asthma is a complex and heterogeneous disease in which a number of pathways can cause reversible airway constriction and increased responsiveness of the bronchial tree to various stimuli. Asthma is characterized by chronic inflammation of

the airways, bronchial hyperactivity, infiltration of the airway submucosa by lymphocytes and eosinophils, and a shift toward a T-helper type 2 (Th2) cell cytokine response. Pathologically, asthma manifests as a widespread narrowing of the conducting airways that leads to the clinical manifestations of paroxysmal cough, dyspnea, and wheezing.

In 2008, 13% of the US population 18 years of age and older had ever been told that they had asthma [1]. There were 3,447 deaths from asthma in the United States in 2007 [2]. It is projected that the direct and indirect costs of asthma to the US economy will reach 20.7 billion dollars in 2010 [3]. The prevalence of asthma more than doubled from 1980 (3.1%) to 2004 (7.1%) [4]. Possible explanations for this increase include changing environmental exposures rather than genetic susceptibility. People are spending more time indoors, and this in turn is leading to greater exposure to house mite dust. Childhood obesity has increased along with a decline in physical activity, which may be a factor. The hygiene hypothesis considers improved hygiene, diminished exposure to bacteria, and widespread antibiotic use as mechanisms of altered exposure to microorganisms [5, 6]. As preterm delivery increases, the use of antenatal corticosteroids for fetal lung maturity increases, which has been independently associated with asthma development [7]. Although several theories provide a potential explanation for the increase in asthma prevalence, this review highlights the role of fetal programming in the development of asthma.

Although genetics and environmental exposures could explain some of the increase in asthma prevalence, a compelling need exists for further investigation into the pathogenesis of this disease. The hypothesis regarding fetal programming or developmental origin of adult disease, also known as the *Barker hypothesis*, proposes that fetal exposure to an adverse uterine environment induces lifelong changes in various organ systems that in turn provide a basis for

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particular diseases later in life. The fetal programming hypothesis may provide new insight into the etiology of asthma.

Fetal Programming

The hypothesis regarding fetal programming, or the developmental origins of adult disease, was initially entertained in the early-1960s, when it was reported that siblings of patients with ischemic heart disease had stillbirth and infant mortality rates twice those of controls. Later studies paved the way for the concept that fetal programming induces lifelong changes in the function of various organ systems, and these changes in turn provide a basis for chronic diseases later in life. The hypothesis received its designation, the Barker hypothesis, after Barker and Osmond [8] found a positive association between current mortality rates from ischemic heart disease and past infant mortality rates. They proposed that poor nutrition in the fetal or early neonatal period increases susceptibility to the negative effects of an affluent diet during adulthood. Additional epidemiologic data and animal experiments produced evidence that a significant correlation exists between malnutrition during the fetal period and coronary heart disease, stroke, hypertension, and type 2 diabetes later in life. Overall, observations evolved into the definition of *developmental plasticity*—the ability of an organism to change its structure and function during critical time windows in response to an environmental stimuli, a process that then becomes irreversible [9].

Fetal Programming and Asthma

Like the fetal programming described in the cardiovascular and metabolic systems, fetal pulmonary and immunologic development may be affected by intrauterine events, particularly transplacental passage of antigens or immunologic signals. Asthma can be triggered early in life by allergies, suggesting an effect of fetal programming on lung development and the immune system. This leads to the following question: are there genetic and environmental factors associated with the diagnosis of asthma? Davidson et al. [10] answered this question by discovering that the risk of developing asthma was positively associated with maternal history of asthma, low socioeconomic status, unmarried status, smoking in pregnancy, short gestational age (24–37 weeks' gestation), low birth weight, black race, forceps or cesarean delivery, male sex, and age younger than 25 or older than 35 years. Coherent with the Barker hypothesis, high socioeconomic status, normal gestational age, and normal vaginal delivery are protective [10].

Effect of Gender

Fetal programming of asthma may be gender specific. Studies demonstrate that estrogen and progesterone modify airway responsiveness. Premenopausal women experience decreases in pulmonary function and increases in asthma exacerbations and hospitalizations during the premenstrual and menstrual phases. Oral contraceptives and hormone replacement therapy are associated with improved pulmonary function and a decrease in asthma exacerbation. Finally, some asthmatic patients experience improved pulmonary function and reduced asthma medication requirement during pregnancy [11].

Parental Effect

Evidence also suggests a parent-of-origin effect. Following maternal inheritance of a polymorphism in the β chain of the high-affinity receptor for IgE, offspring have greater allergen-specific IgE levels and more positive allergy skin prick tests compared with paternal inheritance [12]. Maternal, but not paternal, history of asthma is associated with asthma among children younger than 5 years of age [13]. These findings would suggest that variations in asthma severity according to gender and maternal inheritance of certain genes contribute to asthma development. With the increase in prevalence of asthma during the past 30 years, it seems an association exists between environmental and genetic factors that causes sensitization that eventually leads to clinical disease. The effect may be additive, with the accumulation of inherited genes related to asthma coinciding with exposure to new environmental factors.

Fetal Size

The relationship of fetus size to the development of asthma has been corroborated by several epidemiologic studies. In Hertfordshire, England, lower birth weight was associated with lower mean forced expiratory volume in 1 s (FEV₁), even after adjustment for current height, age, smoking habit, and social class. The association was independent of the occurrence of respiratory infections in infancy. The study concluded that a long-term effect of an adverse environment during a critical period of lung growth represents a form of “programming” [14]. Another study from the United Kingdom found that the risk of asthma in the offspring was inversely related to birth weight [15]. In a 1994 study, the presence of increased serum IgE concentration in adults was found to be strongly related to a large head circumference at birth [16]. A study of individuals born around the time of the Dutch famine (1944–1945) revealed that although prenatal exposure to famine had no effect on total serum IgE concentration, individuals exposed

to famine late in gestation had higher concentrations of specific IgE antibodies against grass pollen [17]. The latter study also confirmed the previously reported association between head circumference at birth and increased total IgE levels in adults. The Maternal-Fetal Medicine Units Network validated this study in 2010 and showed an association between an increase head circumference and birth weight ratio in fetuses as maternal asthma severity progressed [18]. Upon initial review, the previous studies seem counterintuitive toward the development of asthma because the expectation would be for a decrease in asthma with increased fetal head circumference and, thus, fetal size. However, it can be assumed that these findings are related to asymmetric growth restriction, which preserves cerebral blood and head circumference at the expense of shunting blood away from the thoracic cavity. This in turn produces infants that are born with normal head circumference and reduced lung volume. These children would appear to have a large head circumference compared with their body, when in actuality, it is the body that is small compared with the head. In support of this finding, Turner et al. [19] recently evaluated fetal size and asthma in a study that demonstrated an association between decreased fetal size and reduced lung function and an increase in asthma. Shorter crown–rump lengths for gestational age were associated with wheeze and asthma symptoms. In contrast, greater crown–rump lengths for gestational age were positively associated with FEV₁, forced vital capacity, and forced expiratory flow [19]. Based on these studies, a strong association seems to exist between decreased fetal size and the risk of developing asthma.

It is plausible that these differences could be due to environmental or genetic factors. In an ideal situation, these factors could be controlled such that fetal size was the only variable in question. Two important studies last year addressed this question by examining twins [20, 21]. Both found that the risk of asthma increased with reduced birth weight in a cohort of twins and within monozygotic and dizygotic twins. The results suggest that fetal growth restriction affects lung development. Twin studies are unlikely to be confounded by gestational age, shared environment, and genetic factors, which further strengthens the contribution of fetal size to the development of asthma. The studies support the hypothesis that fetal growth influences the risk of asthma development later in life.

Asthma and the Fetal Environment: Experimental Studies

Recent studies have focused on the maternal influence on the immune responses of offspring later in life. The following findings support the existence of mechanisms

for the transfer of immune mediators that could prime or sensitize offspring:

- Presence of antigens in amniotic fluid and cord blood
- Observation of proliferative responses to specific allergens by fetal and infant mononuclear cells
- Detection in umbilical cord blood of IgE antibodies to specific allergens present in the maternal environment
- Increase in cord blood cytokines preceding the development of asthma [22–28].

This evidence supports the theory that the fetus is immunologically exposed to the maternal environment.

Exposure to Allergens

In animal studies, pregnant mice exposed to aerosolized leachate of residual oil fly ash produced progeny with increased airway hyperresponsiveness, increased eosinophils in bronchoalveolar lavage fluid, increased IgE levels in the lung, and increased interleukin (IL)-4 and interferon- γ , suggesting enhanced production of Th2 cytokines [29]. Sensitization of female mice prior to pregnancy and subsequent allergen exposure during pregnancy have been shown to favor the development of allergy in the offspring [30]. Experiments in dogs revealed that the offspring from allergic parents develop allergic sensitization and asthmatic phenotypes when exposed to inhaled allergens, whereas offspring from nonallergic parents do not [31]. Offspring of mice sensitized before breeding and repeatedly exposed to antigen before and during pregnancy demonstrate airway hyperresponsiveness and allergic pulmonary inflammation to the same antigen, as well as to unrelated allergens. Premating treatment of the mothers with anti-IL-4 antibody, or reduction of maternal exposure markedly decreases asthma symptoms in the mice offspring [32]. Pretreatment of pregnant females with interferon- γ results in profound suppression of the airway eosinophilia and goblet cell hyperplasia, as well as reduced levels of IL-4 and IL-5 synthesis by splenic cells in sensitized offspring following antigen challenge [33]. Midoro-Horiuti et al. [34] demonstrated that in mice, maternal exposure to environmental estrogen (bisphenol A) increased allergic sensitization, bronchial inflammation, IgE concentrations, and eosinophilic airway inflammation when pups were exposed to ovalbumin after birth [34]. The evidence suggests that the immunologic outcome of the offspring in response to antigen challenge in utero depends on changes in Th1/Th2 immunity.

In humans, maternal exposure to traffic-related polycyclic aromatic hydrocarbons (PAHs) in New York City was associated with parental report of asthma symptoms in children prior to age 5 years [35]. Administration of antibiotics to the mother has been shown to be associated with an increased risk of asthma in the offspring as well as

in the number of preterm infants born with chorioamnionitis compared with those born without chorioamnionitis [36, 37]. This was confirmed in a cohort study that showed an increase in asthma in children 15–17 years of age who had a intrauterine culture positive for bacteria at cesarean delivery [38]. These findings suggest that environmental exposures and intrauterine microbial growth may increase the risk of asthma development.

At our laboratory, we tested the hypothesis that sensitization of mothers to allergens during pregnancy adversely affects fetal development, leading to abnormal airway function later in life. Pregnant guinea pigs on days 30–35 of gestation were sensitized with an intraperitoneal injection of ovalbumin (100 µg) and aluminum hydroxide (100 mg) in 1 mL of saline. Nonsensitized animals were injected with aluminum hydroxide only. Two weeks after sensitization, all pregnant guinea pigs were tested for sensitivity to ovalbumin by an intracutaneous injection of ovalbumin (0.01 mg in 0.1 mL of saline). Sensitized pregnant guinea pigs developed significant erythema and edema at the site of ovalbumin injection within 24 h, whereas the nonsensitized pregnant guinea pigs had no skin reaction (Table 1). Fetuses in the sensitized mothers therefore were subjected to an environment that included ovalbumin antigen and ovalbumin-specific antibodies, whereas litters in nonsensitized mothers developed in a physiologic maternal environment. All pregnant guinea pigs delivered at term. Pups were weaned from their mothers at 3 weeks of age. At 3 months of age, the offspring were tested for sensitivity to ovalbumin by intracutaneous injection (the same procedure used in the mothers). Offspring born to sensitized mothers developed significant skin thickening and erythema at the site of intracutaneous ovalbumin injection, but no reaction was noted on the skin of offspring whose mothers were not sensitized (Table 1). These findings indicate that sensitization to ovalbumin must have occurred in utero to the maternally administered antigen, as the offspring were never pre-exposed to the antigen postnatally. This conclusion is plausible because ovalbumin has been shown to cross the maternal–fetal barrier [24]. Rings were isolated from the

trachea of 3-month-old male offspring and mounted for isometric tension measurements. Tracheal rings were exposed to ovalbumin (150 µg/mL) to evaluate tracheal smooth muscle responsiveness to antigen challenge. The addition of ovalbumin into the organ chamber significantly increased tension in the trachea from animals whose mothers were sensitized to ovalbumin during pregnancy, whereas no changes were noted in the tracheal tissues from guinea pigs born to nonsensitized mothers (Fig. 1). Our study supports the hypothesis that early fetal development and programming plays a role in asthma.

Exposure to Maternal Malnutrition

Studies have reported on the effects of maternal malnutrition on the immune and respiratory systems of adult offspring. In humans, increased maternal intake of vitamin E is associated with greater crown–rump length for gestational age and a reduction in asthma symptoms in offspring. Low maternal intake of vitamin E during pregnancy is associated with reduced postbronchodilator FEV₁, increased macrophage cyclooxygenase-2 activity, increased production of prostaglandin E₂, and an increased likelihood of asthma development in children at age 5 years [39, 40]. Low-fat diets fed to pregnant rats induce changes in the glutathione-related metabolism (one of the features of the acute-phase response), which lead to more pronounced lung injury in their offspring as compared with those born to mothers on normal diets [41, 42]. Nutrient deficiency and excess can have similar effects. Mice supplemented with a methyl-rich diet showed an increase in asthma severity that was inherited by their offspring. The dietary modification excessively methylated

Table 1 Results of skin testing

Group of guinea pigs	Nonsensitized ^a	Sensitized ^a
Pregnant mothers		
Skin redness, mm	0	24.8±1.1 ^b
Skin thickness, mm	2.8±0.4	5.9±0.3 ^b
Offspring		
Skin redness, mm	0	30.8±2.5 ^b
Skin thickness, mm	3.6±0.2	7.0±0.4 ^b

^a Values presented as mean ± SEM

^b Represents *P* value <0.05

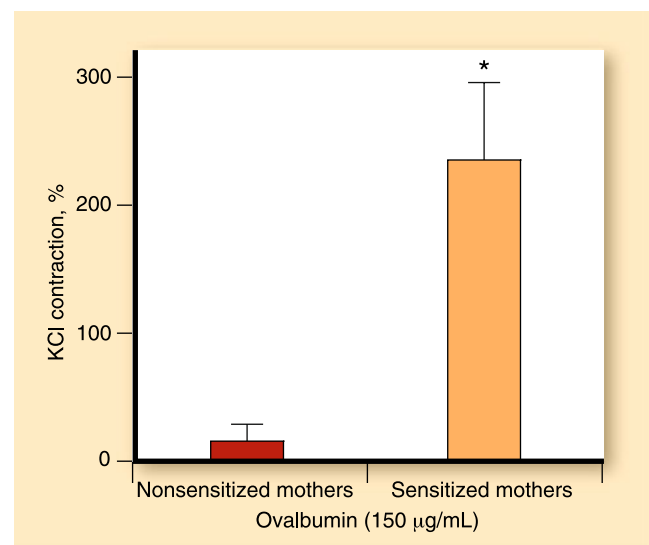


Fig. 1 The effect of ovalbumin on the tracheal rings from offspring born to ovalbumin-sensitized and nonsensitized guinea pigs. Values are presented as mean ± SEM. Asterisk represents *P* value less than 0.05

and suppressed protein levels of *Runx3*, a gene known to negatively regulate airway disease. This treatment caused airway hyperreactivity and high concentrations of serum IgE in the offspring [43]. It is apparent that the nutritional environment present during fetal development contributes to asthma development.

Exposure to Maternal Smoking

Maternal smoking causes fetal hypoxia from increased carboxyhemoglobin and reduced blood flow to the uterus, placenta, and fetus. Health risks associated with smoking during pregnancy include intrauterine growth restriction, placenta previa, preterm premature rupture of membranes, increased risk of sudden infant death syndrome, and abortion placenta. Similar to the effects in humans, maternal smoking in rodents decreases the expression of genes involved in lung development and increases airway remodeling in offspring [44]. Rats exposed to maternal smoking have higher rates of fetal growth restriction and lung hypoplasia with reduced lung volume and fewer saccules, which in turn reduces the surface potentially available for gas exchange [45]. Smoking during pregnancy increases childhood risk of asthma development in the first 5 years of life. Women who quit smoking prior to pregnancy are not at increased risk of their child developing asthma. It is plausible that an epigenetic mechanism may be a factor in the development of asthma, as grandmaternal smoking during the mother's fetal period is associated with increased asthma in her grandchildren [46]. Fetal exposure to tobacco smoke and passive smoking after birth decreases lung function parameters such as FEV₁ and peak expiratory rate in school-age children [47, 48].

It may be possible that the reduction in fetal size caused by smoking—and not smoking in and of itself—is the reason for an increase in asthma seen in offspring. Dezateux et al. [49] addressed this in a study that observed reduced FEV₁ and forced vital capacity in low-birthweight infants and in infants whose mothers smoked while pregnant, suggesting that fetal size and exposure to smoke are independent risk factors for the development of asthma. The timing of tobacco exposure and risk of asthma also have been evaluated.

Alati et al. [50] studied female children whose mothers smoked during pregnancy and in the months following birth. They found an increased risk of asthma symptoms in adolescence; however, in utero exposure to heavy smoking was found to be more significant than postnatal tobacco exposure [50]. The most important association with smoking and adverse outcomes is the increased incidence of sudden infant death syndrome in children whose parents smoke. In a study that evaluated infants who died from sudden infant death syndrome, tobacco smoke exposure in utero that continued postnatally was found to increase the distance between alveolar attachments in intraparenchymal airways. In infants with only postnatal exposure, this distance was not different. This finding is coherent with the above-mentioned study that evaluated alveoli development in rat offspring exposed to maternal smoking [51]. The deleterious effects of smoking during pregnancy are well-known. These studies provide clarity into the relationship of fetal size and smoking, describe a pathological association between smoke exposure and airway remodeling, and highlight that the risk of developing asthma is highest for children exposed to tobacco during development, further supporting the role of fetal programming in asthma development.

Mechanisms of Fetal Programming in Asthma

Gene–environment interactions are the most plausible causes leading to fetal programming of asthma [52]. It has been determined, for example, that *ADAM33*—an asthma susceptibility gene—could be regulated by maternal allergy or exposure to exogenous IL-13 [53]. In general, studies into the developmental origins of adult disease suggest that epigenetic changes take part in the complex of gene–environment interaction [54, 55]. Epigenetic changes (alterations in gene expression that occur in the absence of alterations in DNA sequences), such as DNA methylation, acetylation, histone modifications, changes in microRNA, and chromatin alteration, have been proposed as a mechanism by which fetal programming influences the development of asthmatic phenotype [56•]. These processes have been shown to be

Table 2 Determinants of asthma risk

Environmental	Social	Genetic
Infection/antibiotic exposure [36–38]	Unwed mother [10]	Maternal history of asthma [13]
Prematurity [7]	Low socioeconomic status [10]	Black race [10]
Fetal size [14, 15, 19]		Male offspring [10]
Smoking in pregnancy [10]		Maternal inheritance of polymorphisms [12]
Operative delivery [10]		
Vitamin E intake [39, 40]		
Polycyclic aromatic hydrocarbons [35•]		

involved in T-cell—major effectors of immune response—differentiation [57]. A study published in 2009 in *PLoS ONE* examined the relationship of DNA methylation of *ACSL3* to prenatal exposure to airborne traffic-related PAHs and the development of childhood asthma [35•]. Authors reported that methylation of the *ACSL3* 5'-CpG island was significantly associated with maternal airborne PAH exposure exceeding 2.41 ng/m³ and with a parental report of asthma symptoms in children prior to age 5 years. *ACSL3* belongs to a family of genes involved in fatty acid metabolism. It is expressed in lung and thymus tissues. Authors propose that hypermethylation of this gene in Th cells or lung tissues could diminish the use of fatty acid and β -oxidation energy production and could therefore influence membrane phospholipid composition. Although the direct effect on asthma is unknown, it had been shown that fatty acid composition in the food affects the development of allergy, including asthma [58]. This report provides support for the epigenetic mechanisms for the fetal programming of asthma. Other genes are also possible candidates for epigenetic modulations, such as a recently reported novel gene, *CBE1*, involved in ciliogenesis and early lung development [59]. The general belief is that the study of environmental epigenetics will help us understand a preventable environmental disease.

Conclusions

In summary, asthma is one of the most complex diseases. Studies suggest that asthma risk is determined by genetics, environment, and by prenatal or early-life exposures (Table 2). Epigenetics is emerging as a possible mechanism in the development of asthma. Research into epigenetic modifications, the time during fetal developmental when individuals are the most vulnerable to insults leading to epigenetic alterations, how epigenetics and genetics interact, whether epigenetic changes are modifiable, and so many other questions ultimately will lead to efficient treatment of asthma.

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