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COMMENTARY

Perinatal Events, Vitamin D, and the Development of Allergy

Commentary on the articles by Kero *et al.* and Pichler *et al.* on pages 6 and 12

ISABELLA ANNESI-MAESANO

Respiratory Epidemiologist, INSERM U472: Epidemiology and Biostatistics, 16 ave P. Vaillant-Couturier F94807 Villejuif CEDEX, France

Observational data have suggested that, in addition to genetic liability, intrauterine and perinatal factors also influence the development of asthma and other allergic diseases beyond childhood (1–4). Evidence was produced that: *1*) the number of cord blood T cells was raised after stimulation with specific allergens in newborns who later developed allergic symptoms to those allergens (5, 6); *2*) children of mothers who smoked during pregnancy had a higher risk of developing asthma later in life (7–10), probably because passive smoking is responsible for reduced lung function, lower birthweight and prematurity also associated with childhood asthma (4, 7, 10–12); *3*) asthma and other allergic diseases in children were more frequently reported by mothers when there had been maternal health complications during pregnancy, labor or delivery (4, 7) including caesarian section (CS) (13) or neonatal illness in the 1st week of life (7); *4*) the risk of asthma was increased with early and threatened labor and malpresentation and malposition of the fetus (7, 10); and lastly *5*) newborns with a greater head circumference (corresponding to disproportionate fetal growth) had higher serum total immunoglobulins E (IgE) at birth (14) and in adulthood (15) as well as a higher risk of developing asthma (16). A much stronger transmission of asthma and other allergic diseases to the offspring by the mother than by the father (17) seems to reinforce the suggestion that early life is important in the development of allergy. Maternal transmission of an allergic disease could be explained by stronger maternal heritability as well as environmental events that affect the fetus *in utero* and in the first year of life.

In this issue of *Pediatric Research*, Kero *et al.* contribute to the evidence of a relationship between asthma and early life events by presenting their epidemiologic observations according to which CS is associated with the development of asthma in childhood but not with objective markers of atopy (*i.e.* skin prick test positivity or IgE) (18). The finding that CS is related to asthma in childhood is supported by other methods used by Kero *et al.*, since selection and information biases were avoided and main confounders controlled for in their study. The observed parallel increase in CS rate and asthma calls for a better understanding of the direct role played by this mode of delivery. Originally, caesarean delivery was thought to be responsible for asthma in the offspring due to the use of general anesthesia, which might damage immature airways thereby placing the child at a higher risk of developing bronchial inflammation and asthma (19). Although the study of Kero *et al.* did not take the mode of anesthesia into account, other population-based studies have not found any effect of anesthesia on the incidence of asthma (7) after adjusting appropriately for confounders.

It has been suggested that the mode of delivery is crucial to neonatal development. In particular, labor has been considered as beneficial for lung function growth and immunity maturation (20). By impairing neonatal lung function and hampering immunity promotion, CS could predispose the child to the development of asthma. Furthermore, the type of delivery seems to coincide with a switch from innate immunity (*i.e.* all those elements of the immune system with which an individual is born and/or which are supplied by maternal colostrum and milk) to acquired "cognitive" immunity, which is necessary to protect the child from external aggression. Infants born by CS present significantly lower values of blood neutrophils, monocytes, natural killer cells, and hematocrit than infants delivered vaginally (21). In addition, the compositional development of the primary intestinal microflora, which is crucial to the induction of the oral tolerance necessary for stimulation of the immune system in early life, is delayed up to 6 mo in children born by CS (22). Oral tolerance is able to diminish the Th2-like profile and promote Th1-like one by inhibiting IL-10 and TGF-β mediators (23), thereby protecting the child from the development of IgE-mediated allergy.

The picture of a dual immune response to foreign antigens in newborns has emerged during the last decade, and is based on two different patterns of cytokine production by activated Th cells, the Th1 and the Th2 cells respectively (24). The Th1-like cells preferentially produce IFN-γ and cytokine IL-2 (IL-2) that promote the defense against microbial and viral infections. The Th2-like cells preferentially secrete cytokines IL-4, IL-5, IL-10, and IL-13 that participate through various mediators in the recruitment and the maturation of allergic effectors (namely eosinophils and macrophages) and the production of total and

specific IgE, typical of allergic response. Although the Th1-like cell system has been shown to be naturally predominant, immunomodulation of the naïve immune system toward Th2-like cells is possible under the action of certain factors.

However, it can be also hypothesized that CS is responsible for the inhibition of the Th1-like profile due to the lack of newborn's exposure to infectious agents during the delivery, which could constitute another source of stimulation of the immune system. Additionally, CS is recommended in the case of maternal infections to prevent any transmission of infections to the newborn. According to the so-called "Hygiene hypothesis." the decline in the prevalence of infections could be responsible for the recent epidemic in asthma and other allergic diseases ("Allergy epidemic") (25). Various "proxies" of infections (sibship, birth order, day care attendance, Steiner's lifestyle. . .) are inversely associated with the development of allergy in population-based samples (26). Furthermore, the prevalence of viral and bacterial antibodies have been inversely related to the prevalence of respiratory allergy (27). However, it has been reported that children have a higher risk of asthma (after adjusting for other covariates) if their mothers had experienced maternal vaginitis and febrile infections during pregnancy, particularly in the first trimester, in a population-based sample where the mode of delivery was not taken into account (28). This might be due to *Candida albicans*, which has an allergenic power (29), but further studies are required.

The incidence of allergic diseases has also been related to early vitamin D exposure, mainly because of ecological observations according to which supplementation of vitamin D has been paralleled by an increase in the incidence of allergic diseases (30). This could happen through Th1 inhibition and thereby Th2 production, as shown by experimental data on cytokine production of Th2 cells derived from peripheral cells of adults (31–34). However, an experimental investigation by Pichler *et al.* in this issue of *Pediatric Research* (35) shows that perinatal exposure to vitamin D acts as an immunoregulatory hormone on the maturation of the immune system by interfering with cytokine production of monocytes and lymphocytes, including those involved in the development of IgE-mediated allergy. Apparently in contrast with previous data, the observations of Pichler *et al.* may be explained by the fact that the effects of vitamin D might differ between naive T cells (expressing the CD45RA+ phenotype at the beginning of the "allergic cascade") and more mature cells. Furthermore, it cannot be excluded that a certain amount of vitamin D and thus a latency in the occurrence of its effects are needed to observe Th1 inhibition. This unique experimental observation about the absence of an early effect of vitamin D on cord blood IgE production needs to be replicated by further studies conducted in cohorts of newborns followed-up longitudinally to better elucidate the role of vitamin D supplementation in allergies.

To be extremely cautious in making inferences on the relationship between early life events and allergy, it is worthwhile to explore alternative hypotheses for the observed relationships. It is possible that factors associated with CS or the consequences of CS explain the relationship observed. CS has been related to maternal obesity (36), a predictor of childhood obesity, which has been associated with the development of asthma (37). Thus, the relationship between CS and asthma might relate to the effects of obesity on immunity and airways changes. This could not be verified in the study of Kero *et al.* where anthropometrical characteristics were not exhaustively accounted for. CS could also be a proxy of the severity of maternal asthma during pregnancy. Although the data are limited, CS rate was significantly increased in asthmatic mothers when compared with healthy controls (38). However, this would explain the association only in children with a familial predisposition of asthma. Lastly, CS has been related to an increased risk of posttraumatic stress reactions and maternal stress (39) that might affect the development of asthma in a child. In contrast, variations in the ratio of emergency and elective CS described even in industrialized countries due to differences in health systems (40) (including the fact that sometimes CS is performed for nonmedical reasons in which physician's convenience plays an important role), do not seem to explain the observed association between CS and asthma. Regarding vitamin D, it cannot be excluded that the effects associated with supplementation of vitamin D are due to the intervention of genetic, individual or environmental factors related to it, which have not been examined up to now. Alternatively, it is possible that allergic susceptibility may be responsible for the occurrence of early life events such as those considered here. As a consequence, it cannot be excluded that the observed substantial improvement in maternal and neonatal morbidity accounts for an increase in host susceptibility conferring a higher risk of developing allergic disease. Additional evidence of the association between increased host susceptibility and allergy is provided by the fact that in various studies prematurity and low birthweight ($<$2500 g) have been related to the development of allergic diseases (4, 7, 10–12).

These studies on the role of early life events provide additional information on the relation between asthma and allergy. Above all, the classical paradigm according to which asthma is exclusively linked to the production of specific IgE antibodies to environmental allergens needs to be reconsidered. This is supported by the lack of a clear association of early life events to objective markers of atopy (10, 12, 18), suggesting different programming for allergic phenotypes, although the precise mechanisms are yet unknown. Asthma and the allied affections can be seen as a developmental disease. And early life events might act directly on the target organs of allergy (namely nose, lung, eyes. . .) by involving their structure, cells, mediators and functions. That the paradigm is not unique has already been shown in two different ways. The population-based proportion of asthma cases that are attributable to atopy is usually less than one-half (41). Furthermore, there exist areas in developing countries where a high prevalence of atopy is associated with an exceedingly low prevalence of asthma (42). Hence, the influence of early life factors provides additional evidence that allergy depends on a complex interaction between various genotypes and environments.

Whether the intervention of early life events provides potential explanations for the "allergy epidemic." for which direct environmental causes cannot be identified, remain still to be assessed. Ecological studies have shown that industrialized countries have experienced significant changes in antenatal and

perinatal outcomes concurrently with an increase in the incidence of allergy. Thus, infertility has been largely overcome, pregnancies have proceeded to term more often, the CS rate has dramatically increased (40), and vitamin D supplementation has been introduced early in life for the prevention of rickets. However, confirmatory investigations are required before refuting or accepting the challenging hypothesis according to which the allergy epidemic might be attributed to changes in early life events. Such investigations should necessarily include studies of biologic and physiologic mechanisms.

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