Neonatal Infant Interventions to prevent Asthma and Allergic diseases

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Introduction

Allergic diseases have been increasing during the last three decades, and exact reasons for this worldwide increase in allergy are still debated. Despite intense ongoing research, a lot of aspects of allergic diseases are still poorly understood, resulting in limitations in the current therapeutic approach to allergies. Different interventions to prevent allergies have been studied.

Preventing allergies

The optimal approach to allergies is to prevent them from becoming clinically expressed. A number of primary preventive measures have been investigated during the last decades. Most studies have focused on avoidance of allergens. Based on this, studies on primary prevention measures have specifically targeted nutrition and environmental control in newborn babies *(1-3)*. A summary of the findings is shown in the Table, and were reviewed by Hamelmann *et al*. *(4)*. Prolonged breast feeding (up to 6 months) seems to be still the best, but unable to completely prevent the development of allergy *(5)*.

On the other hand, over the last years a new concept of primary prevention has progressively emerged, which proposes that early exposure to allergens, such as house dust mites and pets, might be able to induce tolerance *(6-9)*. Therefore, a solution for the future might be a controlled exposure to important allergens, as can be achieved by specific immunotherapy, such as subcutaneous immunotherapy (SIT) or sublingual immunotherapy (SLIT). The role of bacterial products (i.e. probiotics, prebiotics, and synbiotics) in primary prevention is still a matter of debate. Most studies show positive results (i.e. publication bias?) on eczema, but not on IgE-mediated immune responses or on respiratory allergies. In some studies, however, no effect was found; while in other an increase of allergic sensitization was demonstrated *(10-12).* Therefore, more research on this important topic is certainly needed. Interventions of primary prevention can be divided into: interventions during pregnancy (prenatally) and interventions during early life (postnatally). Both types of interventions have been reviewed in the literature *(4, 13)*. Most studies have been performed on postnatal primary prevention, while only a few intervention studies during pregnancy were published *(13)*.

- RECOMMENDATIONS DURING PREGNANCY

T-cell conditioning, including allergic build-up, seems to start prenatally *(14, 15).* Although only a limited number of studies have been published on prenatal interventions, the following interventions during pregnancy have been reported:

1) Studies on bacterial load during pregnancy

It has been shown that maternal exposure during pregnancy to an environment rich in microbial compounds (i.e. living on a farm) might protects against the development of atopic sensitization in the children *(16, 17).* In the classical study by Isolauri's group, administration of probiotics during pregnancy and postnatally during 6 months (during prolonged breast feeding of formula feeding) was able to reduce the prevalence of eczema with about 50%, but had no effect upon IgE-mediated hypersensitivity or upon the subsequent development of respiratory allergy (asthma, rhinitis) *(18)*. In another study from New Zealand, supplementation with *Lactobacillus rhamnosus*, but not with *Bifidobacterium animalis*, was able to reduce the prevalence of eczema, when started during pregnancy and continued during 6 months of breast feeding *(19)*.

2) Studies on allergen avoidance during pregnancy

Only a limited number of studies were published on allergen avoidance during pregnancy (avoidance of house dust mite, avoidance of eggs, peanuts and cow's milk) and no beneficial effect was shown *(20, 21)*. In contrast, increased sensitization in the offspring was found in a number of them *(reviewed in reference 13)*. A Cochrane review concluded: "*the* p*rescription of an antigen avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her child's risk of atopic diseases, and such a diet may adversely affect maternal and/or fetal nutrition" (22).*

3) Other interventions during pregnancy

Usage of paracetamol and antibiotics during pregnancy has been associated with an increased risk to develop asthma and allergy in the offspring *(23, 24).* There is limited information that administration of vitamin D and fish oil supplementation to pregnant women might have an inhibitory effect on the development of allergy in their children. However, more studies are needed before this can be recommended *(13, 25).*

- RECOMMENDATIONS DURING BREAST FEEDING

There are no studies showing that any maternal diet is beneficial on the prevention of allergy during breastfeeding *(26, 27).* Birth cohort studies from Denmark suggested that daily intake of cow's milk (by the mother) via breast milk may be beneficial and facilitate tolerance induction to cow's milk *(28)*. In the same studies, however, the administration of supplement cow's milk-based formula during the first 5 days in the newborn nursery increased the risk of specific sensitization *(29)*. Maternal intake of other foods, such as egg, peanut or seafood seems to have no impact upon allergic sensitization of the child *(27)*.

- CONCLUSION AND RECOMMENDATIONS ON PREVENTING ALLERGIES

Preventing allergies has failed so far. Currently, during pregnancy and breast feeding a normal balanced diet is recommended, without any specific modifications.

However, better studies are needed on primary prevention and on the early events of allergic diseases. Interventions should be safe, and without any risk of altering other immune functions. Therefore, it is very unlikely that any medication is a candidate for it. Interventions should mainly involve life style and the usage of natural products, such as bacterial products or allergens. Briefly, the following issues should be addressed in future research:

1. The mechanisms of the initiation of allergic reactions in newborns is still a field that needs to be unraveled (i.e. which genes, epigenetic mechanisms, molecules and cells are responsible for the onset of allergy, preferentially looking at specific allergy profiles).

2. The exact role of bacterial products (probiotics, prebiotics, and synbiotics), including the best type of bacterial product, best dose, and best window of administration.

3. The exact role of early allergen exposure, including whether high allergen exposure is able to induce tolerance to allergens (including the role of early administration of immunotherapy, such as sublingual immunotherapy (SLIT)). This should be studied prenatally and / or postnatally.

4. Breast milk will always be the best, and no other milk or formula will ever be able to replace breast milk. Therefore, studies should be set up aiming to make breast milk more anti-allergic. Indeed, in a number of studies it was shown that high levels of IL10 and TGF-beta in breast milk have a suppressing impact on allergic sensitization in infants *(30)*. Candidates to make breast milk more anti-allergic are immunotherapy, bacterial products and worm antigens (!), administered during lactation.

5. Epidemiological studies to better understand the differences between population differences (i.e. urban *versus* rural), helping to elucidate mechanisms.

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Table: <u>Primary prevention strategies and their outcome</u>

STRATEGY	OUTCOME
Prolonged breast feeding	Breast feeding is useful for the child's health and may prevent allergic sensitization in early life. However, there is no clear benefit for the development of inhalant allergies later in childhood.
Hydrolyzed formula feeding (HA-milks)	Hydrolyzed formulae in young at-risk infants reduce the incidence of food allergy and eczema up to the age of 3 – 5 years, but have no benefit beyond the sixth month of life. Hydrolyzed formulae should be recommended in cases where it is impossible to give breast feeding
Delayed introduction of solid foods	There is no evidence that delayed introduction of solid food after 6 – 8 months of life is useful to prevent food allergy
Avoidance of indoor inhaled allergens	Contradictory results. Reduction of exposure to indoor allergens (house dust mites) might even increase the risk for allergy and should not be recommended. Early exposure to pets might have a protective effect, but there are no intervention studies
Avoidance of pollution and smoke	Pollution and smoke avoidance is mandatory to maintain respiratory health,

	and may be effective in reducing the risk of asthma and allergy

(References in text)