



An integrative medicine review of primary prevention of allergy in pediatrics

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ABSTRACT

The prevalence of allergic disease has been rapidly increasing in the developed world for over fifty years. The prevention of allergic disease remains one of the most elusive topics in medicine. Integrative medicine emphasizes prevention of disease and utilizes many interventions to help modify long-term outcomes of health. Primary prevention refers to the arrest of manifestations of a disease before they present clinically. Preventing allergy is not simply about preventing sensitization, but also about developing tolerance. This narrative review article will discuss integrative medicine approaches that may help to prevent atopic disease in the pediatric population. It is organized chronologically to aid in counseling patients: 1) prevention during pregnancy and 2) prevention after birth. While research into allergy prevention is in its infancy, Integrative Medicine is well-suited to provide many insights into the prevention and mitigation of atopic disease.

1. Introduction

Worldwide, the rise in prevalence of allergic diseases has continued in the industrialized world for more than 50 years. Sensitization rates to one or more common allergens among school children are currently approaching 40–50 %.¹ The major allergic diseases such as allergic rhinitis, asthma, food allergies and urticaria are chronic and not only cause major disability but are costly to both individuals and society.

Historically, allergen and microbe avoidance in early childhood through copious use of hand sanitizers and disinfectants were thought to impart a degree of protection from disease, infection, and allergy. While this is true to a certain degree, particularly in the time of COVID-19, accumulating scientific evidence indicates that allergen avoidance is not the right strategy to reverse the rising prevalence of allergic diseases and may have unintended long-term consequences.

When Dr. Gideon Lack and his colleagues published the now famous Learning Early About Peanut Allergy (LEAP) trial in 2015, in which early peanut introduction was shown to help prevent allergy, the field of Allergy was turned on its head. The study demonstrated that one of the major keys to allergy prevention was not avoidance of the allergen, but rather early exposure.² The concept of exposing the immune system early in life seems to be one of the most important modifiable factors in

overall allergy and asthma prevention.

In addition, research on atopy shows that preventing allergy is not only about preventing sensitization, but also about developing a robust immune tolerance. It is in this intricate interplay of two different arms of the immune system that allergy can develop but can also be mitigated. Integrative Medicine seeks to find benign yet effective interventions to help manage and prevent diseases using many diverse modalities. We will review these modalities, within the field of integrative medicine that may help protect the immune system from insults that may result in atopic disease.

We have organized this paper into two sections. The first half explores preventative measures that can be taken during pregnancy, while the second half looks at interventions after birth.

2. Prevention during pregnancy

2.1. Maternal diet

The role of maternal diet and its influence on atopy offspring has been a growing area of research, and while there are still no clear conclusions, it is becoming more apparent that a healthy anti-inflammatory diet will likely benefit both the mother and her future child.

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In 2019, a French study surveyed over 1,100 women and found that the more cooked green vegetables mothers ate prior to pregnancy, the less likely their child was to develop asthma. They also found pre-natal dietary factors that decreased the development of allergic rhinitis in offspring: greater consumption of cooked eggs and raw vegetables (both before and during pregnancy); increased grains in the diet before pregnancy; and more cooked vegetables during pregnancy. Interestingly, meat intake prior to becoming pregnant was found to be associated with higher rates of wheezing, allergic rhinitis, and atopic dermatitis in offspring.³

Other data are less definitive. A 2018 study from Ireland, which looked specifically at the consumption of oily fish and vegetables during pregnancy, found an inverse association with asthma in offspring, but the confidence interval overlapped 1.0.⁴ A large meta-analysis that examined data from 18 studies in the US and Europe found no association between the amount of fish consumed during pregnancy and wheezing and asthma in children.⁵

Trials are still needed to determine the impact of maternal diet on development of atopy in offspring. Despite the lack of firm evidence, yet with no evidence to the contrary, recommending an anti-inflammatory diet both prior to pregnancy and during pregnancy will likely aid in mitigating some features of atopy in children.

2.2. Avoidance vs consumption of allergenic foods during pregnancy

Another active area of research is examining whether consumption or avoidance of allergenic foods such as peanut, soy, dairy and eggs plays a role in future allergies of offspring. One study showed that major food allergens can be detected in amniotic fluid.⁶ Whether or not this exposure plays a role in the development or prevention of allergy remains unclear.

A large review in 2012 concluded that maternal avoidance will not confer protection from future food allergens.⁷ As of now, no major organizations (including the AAP or American College of Obstetricians and Gynecologists (ACOG)) recommend maternal elimination of allergenic food diets as a means of preventing future food allergies in offspring.

2.3. Dietary supplements during pregnancy

In 2016, the World Allergy Organization (WAO) reviewed evidence for the use of vitamin D, prebiotics, and probiotics for the prevention of allergic disease.⁸ Their systematic review of available evidence found no support for the hypothesis that vitamin D supplementation reduces the risk of developing atopic disease in children. The review did not include a trial published that same year which demonstrated decreased wheezing by 6.1 % at 3 years of age following maternal vitamin D supplementation, however this result did not reach statistical significance.⁹

Gut health is an active topic of research in allergy and immune modulation. Intestinal microbiota may modulate immunologic responses and thus influence development of allergy. The WAO guidelines recommend using prebiotic supplementation only in not-exclusively breastfed infants, and probiotics in pregnant and lactating women and infants when there is a high risk of allergy in children (defined as presence of biologic parent or sibling with asthma, allergic rhinitis, eczema, or food allergy).^{10, 11} It is important to note these recommendations were noted to be conditional and based on low quality evidence. Additionally, no guidance was provided in regard to timing, duration, and choice of probiotic. Given the heterogeneity of the available studies and the variability in results, other expert bodies such as the US National Institute of Allergy and Infectious Diseases have not given any specific recommendations on these products.

Another maternal diet supplement that has been studied for the prevention of atopic diseases in children is a group of dietary fats that include essential fatty acids: Omega-3, 6 and 9. While basic science and animal models strongly suggest a protective role of supplemented

polyunsaturated fats (PUFAs) in the primary prevention of allergic disease, the clinical data is less clear. A 2015 Cochrane review did not find definitive evidence that supplementation was substantively correlated to preventing allergies in children.¹²

2.4. Maternal stress

A systemic review conducted in 2015 demonstrated a growing number of studies which suggest that maternal stress such as negative life events, anxiety/depression, bereavement, distress, and job strain during pregnancy promote the development of atopic disease in offspring.¹³ It has been suggested that gestational exposure to maternal stress alters the development of the humoral immune system in the fetus and the hormonal and immunological responses to stress in postnatal life, thus implicating a risk of developing atopic disorders.^{14, 15}

Elevated levels of IgE and T-cell sensitization to dust mite has been shown in 3-year-old children who were exposed to maternal stress in utero.¹⁶ An inner-city birth cohort showed higher rates of wheezing episodes by age 1 in children born to mothers with high levels of perceived stress or depression.¹⁷ Further research is needed to assess whether stress-reducing interventions like mindfulness/meditation, prenatal yoga, or cognitive behavioral therapy can help to prevent atopic disease in children.

2.5. Maternal smoking

Cigarette smoking during pregnancy represents the single greatest modifiable risk for all pregnancy-related morbidity and mortality. In addition to preterm birth, cognitive delays, preterm/still birth, intra-uterine growth restriction, and a multitude of postnatal adverse outcomes, prenatal smoking is highly associated with atopic disease. Prevention and cessation of tobacco smoke exposure during pregnancy has been the one factor that has repeatedly and consistently shown to reduce asthma in every population in which it has been studied.¹⁸

2.6. Cesarean sections

Several studies have demonstrated that children born by caesarean section (c-section) are at a greater risk for several diseases compared to their vaginally born counterparts. In a cohort obtained through the Danish national registry over a period of thirty years, c-sections were found to be associated with a number of disorders associated with immune dysregulation such as asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, immune deficiencies, and leukemia.¹⁹

It has been shown that passage through the vaginal canal alters the microbiome of a newborn child. Newborns who are born via c-section have an intestinal microbiome similar to surrounding environmental microbes. Those born vaginally have a microbiome similar to the maternal vaginal and intestinal contents. The role of commensal bacteria in immune development is only being fully elucidated upon now, but it is clear that these differences in diversity may lead to different clinical outcomes.²⁰

This information has led several researchers to investigate “vaginal seeding,” the act of inoculating a cotton swab with vaginal fluids and wiping it on the mouth nose or skin of the newborn infant with the goal of transferring the maternal microbiome to the child to help prevent neonatal dysbiosis. Further research is still needed, but vaginal seeding may provide a protective measure against atopic disease. Currently, ACOG does not recommend its use outside of clinical trials.²¹

3. Prevention after birth

3.1. Hygiene hypothesis

The “Hygiene Hypothesis” is a theory suggesting that modern

industrialized environments fail to provide necessary exposure to pathogens required to effectively develop an immune system. When the hypothesis was introduced in the 1980s as an explanation of the growing epidemic of asthma and allergies, it caused a shift from the previous dogma of avoidance as a method of preventing atopy towards that of early exposure. Over the past several decades, this hypothesis has been the subject of many investigations which have raised the awareness of the role of microbial exposures in priming the immune system for adequate and appropriate function.

3.2. Environmental exposure

A classic study exploring the “Hygiene Hypothesis” was published in 2016 and examined the Amish and Hutterites, two agricultural populations in the United States whose lifestyles are remarkably similar in many respects, but whose farming practices are distinct.²² The Amish follow traditional farming practices with single family farms where children play in barns around farm animals versus the Hutterites which use industrialized farming practices where homesteads are away from farmed animals. The study results demonstrated that although Amish children were exposed to bacterial endotoxins at a volume of seven-fold higher than their Hutterite counterparts, they had a four-fold lower risk of developing asthma or allergic sensitization.

Interestingly, the Urban Environment and Childhood Asthma study examined a birth cohort at high risk for asthma and their allergen exposures and bacterial content of house dust collected in the first year of life.²³ Results showed that cumulative allergen exposure over the first three years of life was associated with allergic sensitization, which in turn was related to recurrent wheeze.

While early exposure to certain allergens seems to play an important role in preventing allergic disease and promoting immune tolerance, several questions still remain unanswered, such as how much exposure and what type of exposure. What is clear, however, is that the further we move away from industrialized and urban living, the less likely we are to develop atopic disease. Interacting with animals, organic farms, and being outdoors beginning at a young age confers a degree of protection and immune tolerance.

3.3. Air pollution

Air quality is another factor that has contributed to increased prevalence of atopic diseases in developing countries. While asthma has largely been the focus of studying air pollution and atopic diseases, many studies have also looked at the role of air pollution in the development of allergic rhinitis and atopic dermatitis. Of greatest concern is traffic-related air pollutants (TRAP), which are common in high population density areas, specifically amongst urban and low socio-economic populations. A 2019 review article found growing evidence that suggests significant associations between TRAPs and atopic disease, but further research is still needed.²⁴

3.4. Furred animals

An area of active controversy regarding early exposures to allergens remains the presence of furred domesticated animals in the home, specifically dogs and cats. Given that cat and dog allergens are ubiquitous, even in the homes of non-pet owners, it is very difficult to study their impact. Several systematic reviews have been conducted regarding exposure to domestic pets. One found that dog exposure has no significant effect on the development of asthma, but cat exposure was protective.²⁵ A meta-analysis using 26 publications found exposure to dogs decreased the risk of atopic dermatitis by nearly 25 % and cats conferred no significant protection.²⁶

A Swedish study with over 1 million children enrolled, showed reduced incidence of development of asthma in preschool and school aged children when exposed to dogs or farm animals at early age.²⁷ A

follow-up study by the same researchers showed a dose-dependent relationship, finding less manifestation of allergic disease with increasing number of household cars and dogs during the first year of life.²⁸ Overall, it is difficult to draw any conclusions about the role of furred animals in the prevention of allergy and development of tolerance.

3.5. Viral illnesses

Numerous studies have associated early-life infections, particularly respiratory syncytial virus (RSV) and rhinovirus (RV), with the development of chronic asthma. It remains to be shown whether infection by these viruses is a marker of a genetic predisposition to asthma, whether the predisposition to develop asthma results in increased risk of infectivity, or even if the viruses themselves trigger changes that lead to chronic asthma. These viruses are ubiquitous, easily transmissible, and are common childhood infections. In the case of RSV, biological prophylaxis (palivizumab) has been efficacious against the development of serious RSV lower respiratory tract disease in children at high risk of RSV disease, however, its long-term effect on the development of asthma and recurrent wheezing is not clear.²⁹ More research is needed to elucidate the role of viruses in the development of chronic asthma.

3.6. Breastfeeding

Breastfeeding remains the most recommended source of nutrition for the first six months of life. Not only has it been shown to reduce the risk of infection, sudden infant death syndrome, and childhood leukemia, but it also has shown to have an immunomodulatory effect conferring protection against autoimmunity and allergy.³⁰

The AAP Committee on Nutrition published a clinical update in 2019, which provided insight into the relationship between breastfeeding and atopy.³¹ While the results of over 60 new studies and 3 systemic reviews published on the connection between asthma and breastfeeding were not definitive, the most recent research seems to suggest that breastfeeding has a protective effect against infantile eczema. This effect is limited to the first two years of life and there is no evidence to indicate that the duration of breastfeeding beyond 3–4 months impacted atopic dermatitis in a meaningful way. Interestingly, a trial in 2015 from Iran showed that the short-term topical application of breast milk to treat eczema was equally effective as 1% hydrocortisone in children with mild to moderate eczema who were, on average, 4.5 months old. This alone may provide a reason for continued lactation.³²

A hypothesis has been proposed that early introduction of allergenic foods while breastfeeding may be protective. Unfortunately, no clinical trials comparing introducing of allergenic foods while exclusively breastfeeding versus exclusive formula feeding exist, that would support this claim. Most early introduction trials skew towards populations with exclusive breast feeding. For example, in the LEAP trial 92 % of infants enrolled were breastfed.³³

3.7. Formula supplementation

Formula supplementation of breastfed infants continues to occur during birth hospitalizations for numerous reasons, many of which are not evidence-based nor medically necessary. Not only has in-hospital formula supplementation been associated with increased risk of early breastfeeding weaning,³⁴ but it has also been associated with an increased risk of developing cow's milk allergy.³⁵

3.8. Maternal elimination/integration diet

Though it is clear that protein allergens can be expressed through breast milk, exactly what their role in either the development or prevention of food allergy remains unclear.³⁶

For several years it was suggested that intact food proteins in

mothers' milk may sensitize breastfeeding infants. Despite multiple randomized controlled trials and systematic reviews, researchers have been unable to conclude that an elimination diet during breastfeeding offers any protection from the development of atopic disease. Further research is needed to determine the role of avoiding or integrative allergenic foods into maternal diets, but at this time it is best to advise that mothers maintain their regular diets.

3.9. Dietary patterns

The Mediterranean diet is believed to be the most protective diet with regard to the development of atopy. However, its protective effects have only been shown in cross-sectional studies, and one prospective study could not confirm results.³⁷ Despite the lack of overwhelming evidence to support the use of a Mediterranean diet as a primary preventative tactic in children, it is clear that a modern Western diet with high intakes of fast food, may predispose to inflammatory disease -specifically wheezing and asthma - in a dose-response manner.³⁸

One key difference between the Mediterranean diet and the Western diet is the amount of fruits and vegetables consumed. High intake of fruits and raw vegetables during childhood has been shown to significantly reduce the risk of wheezing and asthma.³⁹ The positive effect of higher intakes of fruit and vegetables on the development of asthma is promising, but well-designed randomized-control trials are still warranted to formulate official society guidelines.⁴⁰

3.10. Early food introduction

In 2015, the LEAP trial showed that in high risk infants, in particular those with severe eczema and egg allergy, early consumption of peanut helped to prevent the development of peanut allergy. Of the children who avoided peanut, 17 % developed an allergy to it by 5 years old. Incredibly, of those who were fed peanut before the age of 11 months at least 3 times a week, only 3% went on to develop a peanut allergy by 5 years old.¹ The LEAP-ON study reinforced the position that early introduction is a safe and effective means of preventing food allergy and helps maintain long term tolerance.⁴¹

Subsequently, other observational studies reported similar findings with regard to eggs, milk, oats, and wheat.⁴² It is also important to know that removal of food from the diet, especially as a means of preventing atopic dermatitis, can lead to loss of tolerance and the development of a life threatening IgE mediated reaction. Food avoidance for treating atopic disease is therefore only recommended in the most severe patients.

3.11. Food processing

Several studies have examined the effects of cooking methods on the allergenicity of certain foods. Chinese children living in China have surprisingly low rates of peanut allergy despite high levels of consumption. In contrast, American-Chinese children appear to have peanut allergies at the same rate as their American counterparts. One of the key differences between how peanut is introduced in these countries is how the peanut is prepared.

It has been suggested that the lower rates of peanut allergies in areas like China may be secondary to how peanuts are traditionally prepared via boiling or frying. In the United States the most common way of cooking peanuts is through roasting. Roasting induces a chemical reaction commonly referred to as the Maillard reaction, which produces advanced glycation end products, which can increase allergenicity of peanuts. Studies have shown that IgE binding to Ara h 1,2 and 3, the proteins most commonly associated with peanut anaphylaxis, was significantly lower in boiled and fried peanuts, in comparison with roasted preparations.⁴³

3.12. Organic food

There have been several studies that suggest a lower prevalence of atopic disease and/or food sensitization in families who adhere to an organic diet. The strongest evidence for this is a prospective study from the Netherlands which purportedly demonstrates that consumption of organic dairy products is associated with lower eczema risk. No such association was found with organic meat, fruit, vegetables or eggs, or the proportion of organic products within the total diet, as related to the development of eczema, wheeze or atopic sensitization.⁴⁴ These studies should be interpreted with some caution, as they do not control for other lifestyle factors, especially for confounders that are associated with overall healthy living.

There is strong evidence to suggest low prevalence of atopic diseases in children raised on traditional farms. The sources of protection to allergic diseases such as asthma and allergic rhinitis has been correlated to consumption of unprocessed cow's milk.⁴⁵ The consumption of raw milk and products thereof has been tied to life-threatening infections and therefore should be strongly discouraged. Investigations are currently underway to determine if minimally processed alternatives to cow's milk also have the same preventative disease properties.

3.13. Supplements

Evidence for the use of supplements in infants as a means of preventing atopic disease is weak and inconclusive. There are exciting findings using certain traditional Chinese herbal formulas to treat some food allergies, but prevention has not been examined as of yet.⁴⁶ At this time the best advice for patients is to obtain their vitamins, minerals and probiotics through a healthy anti-inflammatory diet.

3.14. Vaccination

There has been much speculation about the role of vaccines and the stimulation of the immune system. A German study examining a large birth cohort of 943 children found transient protection against atopy in the first year of life in children with higher vaccine coverage.⁴⁷ A study of 15,000 children from 5 European countries showed that atopic sensitization was inversely associated with measles infection, with a similar tendency seen for measles vaccination.⁴⁸ In 2018, a Swedish birth cohort found no support for an association between early childhood vaccinations and allergic sensitization.⁴⁹ It is fair to conclude that vaccines do not contribute to atopic disease and may in fact help to prevent them.

4. Conclusion: a sensible approach to prevention of atopic disease

Why all forms of atopic disease are increasing in prevalence remains a mystery. A likely factor is the expansion of industrialization and urbanization in our society. The further we move from "natural" living, the more our bodies seem to be impacted by it. This is exemplified in diets which contain extensive amounts of processed foods, our lives in large, polluted cities away from agrarian living, and the incessant need to sterilize all of which we come into contact with. All of these cultural shifts seem to be contributing to the development of allergic disease.

While there is no simple catholicon, there are several interventions one can take to help prevent the development of allergies:

- 1 Get Dirty. Let kids play in the mud and take them to visit farms. Early childhood antigen exposure is essential in developing tolerance to allergens and preventing allergic disease.
- 2 Introduce foods early. There is no benefit to delaying the introduction of highly allergenic foods. In fact, in the case of peanuts and eggs it has shown to be beneficial.
- 3 Breastfeed your infant for at least 3–4 months.

- 4 For cases of mild to moderate eczema in infants try using breast milk prior to topical steroids.
- 5 Quit Smoking. Smoking is the number one modifiable risk factor for atopic disease. Also remove other sources of smoke exposure like incense and vaping.
- 6 Eat a whole food organic anti-inflammatory diet.
- 7 If possible, avoid c-sections. Often times this is not a choice for delivering mothers, but if it is, one should consider the potential risk factors.
- 8 Vaccinate your children. Vaccinations do not contribute to atopic disease, and may, in fact, help prevent it.
- 9 Reduce your stress level. A positive attitude is the greatest prescription for a happy, healthy life.

Declaration of Competing Interest

None.

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