The Impact of Prenatal Nutrition on the Development of Atopic Dermatitis in Infancy and Childhood

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PRACTICE **POINTS**

- The prevalence of atopic dermatitis (AD) has been increasing globally, with a marked increase in developed countries.
- Maternal dietary restriction is not recommended in pregnancy for the prevention of atopic disease in infancy and childhood based on the existing literature.
- There is mixed evidence to support probiotic supplementation in the prenatal period.
- The recommendations supporting antioxidant and fatty acid supplementation as well as specific prenatal diets for the prevention of AD in infants and children are limited due to the heterogeneity of study designs.

Atopic dermatitis (AD) is an inflammatory skin condition characterized by skin barrier disruption and inflammation that has been associated with the development of food allergies, asthma, and allergic rhinitis, known as the atopic march. The prevalence of AD has been increasing globally, with a marked increase in developed countries. Although many studies have examined environmental factors contributing to the development of AD in infancy and childhood, less is understood about the influence of prenatal factors. Several studies have examined the role of maternal diet and nutrition on the development of AD in offspring; however, formal recommendations and robust trial data are lacking. Herein, we examine the existing literature surrounding maternal diet on the development of AD in infancy and childhood.

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Atopic dermatitis (AD) is an inflammatory skin disease characterized by skin barrier disruption, skin inflammation, and pruritus.[1] It is a common and often chronic skin condition associated with the development of food allergies, asthma, and allergic rhinitis, known as the atopic march.[2] Atopic dermatitis is estimated to affect 10% to 25% of children, most with onset before 5 years of age, and up to 7% of adults worldwide.[3] Most patients improve with time, but multiple disease trajectories are possible. Several studies have demonstrated that fewer than 4% of children develop the classic atopic march—AD followed by food allergies, asthma, and finally allergic rhinitis—with recent evidence pointing to a more complex heterogeneous progression of disease and allergic comorbidities often occurring together.[4,5] The prevalence of AD has been increasing globally over the last 30 years,[6] with a marked increase in developed countries.[6,7] It is well accepted that AD is based on an interplay between genetic predisposition and environmental factors,[8] but many suspect that the rapid rise in prevalence cannot be attributed to genetic factors alone.[9] The precipitant triggers for AD remain an area of intense investigation, with ongoing debate between the "inside out" and "outside in" hypotheses; these revolve around whether abnormalities in the immune system trigger barrier dysfunction or barrier dysfunction triggers immune programming to atopy.[8] Ongoing research related to genetic predisposition of AD has identified candidate genes implicated in both impaired skin barrier function and

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altered immune system pathways, further supporting that both theories may contribute to disease pathogenesis.

The increasing prevalence of AD, with increasing disease burden within socioeconomically advantaged countries, raises the possibility of early modifiable environmental factors that may contribute to the disease process.[10] Many studies point to the influence of the 21st century lifestyle and Western diet as primary contributing factors.[9,11] However, it is not clear how these factors may influence the development of allergic atopic disease. Several studies have suggested that nonheritable influences in utero can alter fetus immune function and influence the subsequent development of allergic disease.[12,13] Although many studies have examined environmental factors contributing to the development of AD in infancy and childhood, less is understood about the influence of prenatal factors. Currently, in utero exposure to tobacco smoke, phthalates, and maternal distress have been potentially implicated in the development of AD.[14,15] Several studies have examined the role of maternal diet and nutrition on the development of AD in offspring; however, formal recommendations and robust trial data are lacking. In this article, we examine the existing literature surrounding maternal diet on the development of AD in infancy and childhood.

Allergen Avoidance

Extrapolating from the food allergy literature, it was once suggested that allergen avoidance in early childhood had a protective effect on the subsequent development of allergies; however, more recent research has found that early exposure to common food allergens, such as peanuts or eggs, may actually reduce a child's risk for developing these allergies later in life.[16] Among infants at high risk for food allergy, sustained consumption of peanut products beginning in the first 11 months of life resulted in an 81% lower rate of peanut allergy at 60 months of age than the rate among children who avoided peanuts.[17] Given the results that antigen avoidance during infancy/childhood does not protect against the development of allergies and may actually be counterproductive, it is not surprising that research studying antigen avoidance during pregnancy on the development of AD also has demonstrated limited efficacy. A systematic review of 5 trials on maternal dietary antigen avoidance (N=952) suggested no protective effects of avoiding antigenic foods during pregnancy on the development of AD in the first 18 months of life.[18] Another meta-analysis evaluating 12 intervention trials looked at the effects of maternal allergenic food avoidance during pregnancy or lactation and found no reduced risk for subsequent development of allergic disease, including AD.[19] The American Academy of Pediatrics 2019 consensus statement does not support maternal dietary restrictions in pregnancy for the prevention of atopic disease and makes note that the data remain limited, which complicates drawing any firm conclusions.[20]

Probiotic Supplementation

One of the most investigated dietary supplements for the prevention of atopic disease is probiotics, with possible benefits noted in both the prenatal and postnatal periods. Baquerizo Nole et al[21] examined several studies looking at the various benefits of probiotics in AD, which included inhibition of the helper T cell (T_H2) response, stimulation of the T_H1 response, upregulation of regulatory T cells, acceleration of skin and mucosal barrier function, increase in intestinal microflora diversity, suppression of toxic fermentation products in the intestinal lumen from increased production of short-chain fatty acids, and inhibition of *Staphylococcus aureus* attachment on epidermal keratinocytes. It is unclear how this may affect infants prenatally; however, transfer of maternal intestinal microflora during delivery and shortly thereafter has demonstrated that probiotic strains remain detectable in the infant's stool up to 6 months after delivery, even if the mother has discontinued use.[22] A 2008 meta-analysis of 10 double-bind, randomized, controlled trials (N=1880) looking at the use of maternal prenatal and postnatal probiotic supplementation in the prevention of pediatric AD found a relative risk (RR) ratio of 0.69 (95% CI, 0.57-0.83) using a fixed effects model and RR ratio of 0.66 (95% CI, 0.49-0.89) using a random effects model. After exclusion of one study that evaluated the effect of postnatal probiotic supplementation only, the RR ratio decreased to 0.61 for both the fixed effects and random effects models.[23] A systematic review by Panduru et al[24] noted similar findings with a subgroup meta-analysis of 11 studies of prenatal supplementation followed by postnatal supplementation of probiotics, which demonstrated a protective effect on the development of AD (odds ratio [OR]=0.61, $P<.001$). Postnatal supplementation alone (4 studies) did not have the same association (OR=0.95, $P<.82$).[24] A 2012 meta-analysis by Doege et al[25] evaluated 7 randomized, double-blinded, placebo-controlled trials that assessed probiotic supplementation during pregnancy (without incorporation of postnatal supplementation) and found a significant risk reduction of 5.7% ($P=.022$) for AD in children aged 2 to 7 years. Interestingly, this was only significant for *Lactobacillus* and not for other bacterial strains, even if a mixture of strains included *Lactobacillus*. However, Panduru et al[24] found both maternal *Lactobacillus* supplementation alone (8 studies) and in combination with *Bifidobacterium* (9 studies) was protective against AD development in children (OR=0.70, $P=.004$; OR=0.62, $P<.001$). A more recent 2015 meta-analysis of 17 studies (N=4755) evaluating the use of maternal probiotic supplementation in pregnancy and/or through the infant's first 3 months of life found a significantly lower RR (0.78 [95% CI, 0.69-0.89], $P=.0003$) for the development of AD in infants treated with probiotics and found this risk to be even further decreased when a mixture of probiotics including both *Lactobacillus* and *Bifidobacterium* was used (RR=0.54 [95% CI, 0.43-0.68], $P<.00001$).[26]

Antioxidants

The Westernization of many developing countries' diets—diets high in saturated fats, protein, sucrose, salt, and processed foods and low in fresh fruits and green vegetables—has led to a reduced intake of antioxidants and an increase in susceptibility to oxidative damage.[27,28] One hypothesis suggests that a reduction in nutritional antioxidants and subsequent oxidative damage leads to airway inflammation that may contribute to an increased prevalence of asthma.[27] In vitro data suggest that antioxidant deficiency may influence the differentiation of helper T cells to a T_H2 phenotype, which can increase susceptibility to the development of asthma and allergies.[29] Vitamin E specifically has been shown to inhibit IL-4 gene expression, which drives type 2 immunity and decreases expression of multiple genes that regulate epidermal barrier function, subsequently increasing susceptibility to allergic inflammation and AD.[29,30] Regardless of the proposed mechanisms for antioxidant deficiency increasing susceptibility to allergic disease, studies evaluating the benefits of antioxidant intake during pregnancy in relation to AD have not been promising. Several studies have found no association between prenatal vitamin E intake and the risk for AD development in infants and children.[31,32] Another study found a statistically significant inverse relationship between vitamin E intake in mothers with a history of atopy and the development of AD in their children at 2 years of age but not at 1 year of age (*P*-trend=.024).[33] It has been suggested that varying vitamin E isoforms may contribute to the discrepant results previously discussed, with the γ-tocopherol isoform (found frequently in Westernized diets)[34] as a driver of inflammation in murine models.[35] West et al[31] noted an association between vitamin C intake and development of "any allergic disease"—AD, IgE-mediated food allergy, or asthma—with a crude OR of 0.48 (95% CI, 0.25-0.93). However, the *P*-trend and adjusted OR were not statistically significant. The investigators found no association between maternal intake of beta-carotene, vitamin E, or zinc, but they did find copper supplementation to be protective on the development of AD at 1 year of age (*P*-trend=0.03). Interestingly, when the data for total antioxidant intake—vitamin C, vitamin E, zinc, beta-carotene, and copper from both diet and supplementation—were combined and analyzed, no statistically significant associations for any of the antioxidants were found.[31] Another study of 763 Japanese mother-child pairs found a reduced risk for AD at 16 to 24 months of age with high maternal intake of beta-carotene but found no statistically significant exposure-response associations with other antioxidants, including alpha-carotene, vitamin C, or zinc from dietary intake alone.[32] These results were substantiated by 2 meta-analyses evaluating a total of 93 combined intervention trials and cohorts where no association was found between vitamin or mineral intake during pregnancy and/or during infancy and the development of AD.[19,36]

Fatty Acids

Other dietary changes that are associated with an increased prevalence of atopic diseases in children include excess consumption of omega-6 (n-6) long-chain polyunsaturated fatty acids (LC-PUFA) and insufficient omega-3 (n-3) LC-PUFA consumption.[37] Given prior evidence that allergic immune responses in infants may be primed before birth,[38] researchers have questioned whether the anti-inflammatory properties of n-3 LC-PUFA when supplemented during pregnancy may have immunomodulatory effects on infants that could alter their predisposition to develop allergic disease, including AD.[39] A systematic review and meta-analysis of randomized controlled trials found a statistically significant RR of 0.53 (95% CI, 0.35-0.81; *P*=.004) for the incidence of AD at 12 months of age with maternal supplementation of n-3 LC-PUFA.[9] Another trial of 145 pregnant women randomized to supplementation with fish oil vs placebo starting at gestational week 25 and continuing through 3.5 months of breastfeeding found a reduced cumulative incidence of AD in the intervention group compared to controls at 2 years of age, with a statistically significant crude OR of 0.33 (95% CI, 0.11-0.97; *P*=.04).[40] However, the adjusted OR was not statistically significant. In addition, they found that mothers and infants with higher proportions of docosahexaenoic acid and eicosapentaenoic acid in plasma phospholipids have been noted to have a lower prevalence of IgE-associated disease in a dose-dependent manner (*P*<.05 and *P*<.05, respectively).[40] In another trial of 98 pregnant women randomized to fish oil supplementation or placebo from 20 weeks' gestation to delivery found no difference in the frequency of AD but did note that infants in the exposure group had significantly less severe AD compared to controls (OR=0.09 [95% CI, 0.1-0.94]; *P*=.045).[39] A prospective birth cohort study of 2641 children evaluated dietary composition during the last 4 weeks of pregnancy and found that consumption of foods rich in n-6 LC-PUFAs (eg, margarine, vegetable oil) increased the risk for developing AD, while foods rich in n-3 LC-PUFAs (eg, fish) decreased the risk for developing AD in offspring at 2 years of age. All *P* values for margarine, vegetable oil, and fish were statistically significant on logistic regression at *P*<.05.[41] A longitudinal analysis of follow-up data from a randomized controlled trial looking at maternal prenatal n-3 LC-PUFA intake and the development of allergic disease (including AD) found no differences in the development of disease at 1-, 3-, or 6-year follow-up.[42] Despite several studies demonstrating a possible benefit of omega-3 fatty acid intake on the development of AD in offspring, the longitudinal analysis by Best et al[42] reminds us that long-term follow-up is critical in establishing benefit of any intervention given the heterogeneous and progressive nature of the atopic march and AD.

Specific Diets

Several studies have evaluated the role of dietary patterns and their influence on atopic disease. Studies evaluating dietary patterns or supplement intake can be challenging,

as data often are derived from questionnaires with bias in response to families with higher socioeconomic status.[9] Further, analysis of any one food group does not account for the potential interplay between nutrients.[43] Studies should focus more on dietary patterns vs individual foods to assess true risk.[43,44] Given these limitations, study results on diet should be carefully scrutinized; however, there are still some positive findings that deserve further investigation. Chatzi et al[44] followed 460 children for 6.5 years and found a protective effect for the development of atopy in the offspring of women who had high adherence to the Mediterranean diet (OR 0.55 [95% CI, 0.31-0.97]). Another cohort study evaluating the effects of the Mediterranean diet and risk for AD in the first year of life in 2516 mother-child pairs from Spain and Greece found no statistically significant association with consumption of the Mediterranean diet and AD. The investigators also evaluated intake of fruits, nuts, vegetables, meats, processed meats, dairy products, and cereal and found no statistically significant protective benefit.[45] Another systematic review of more than 90 observational studies identified no significant relationship between prenatal dietary exposures of fruits, vegetables, nuts, fat, fatty acids, eggs, cereal, milk, alcohol, tea, or coffee and risk for allergic disease in offspring, including AD.[19]

A Chinese prospective cohort study evaluated the dietary protein patterns of 713 mother-child pairs and the incidence of infant AD at 6 months of age.[46] Dietary protein patterns were characterized as predominantly poultry, plant based, dairy and eggs, and red meat and fish. The investigators found a statistically significant reduced risk for AD in mothers who consumed plant-based or dairy and eggs protein patterns when compared to a poultry protein pattern with an adjusted OR of 0.572 (95% CI, 0.330-0.992) and 0.478 (95% CI, 0.274-0.837), respectively. This protective effect was not seen with the red meat and fish protein patterns.[46] Similar results were seen in a 2020 Canadian study that evaluated the effects of a Western (fats, meats, processed foods, and starchy vegetables), balanced (diverse sources of animal proteins [especially fish], fruits, vegetables, nuts, and seeds), or plant-based (dairy, legumes, vegetables, whole grains, and an aversion to meats) diet in more than 2000 mother-infant pairs from 24 to 28 weeks' gestation to 1 year of age. The investigators found a lower OR of AD in mothers who followed a mostly plant-based diet compared to other dietary patterns (OR 0.65 [95% CI, 0.55-0.76]; $P<.001$).[10] Another prospective Japanese study looking at healthy (high intake of green and yellow vegetables, seaweed, mushrooms, white vegetables, pulses, potatoes, fish, sea products, fruit, and shellfish, and low intake of confectioneries and soft drinks), Western (high intake of vegetable oil, salt-containing seasonings, beef, pork, processed meat, eggs, chicken, and white vegetables, and low intake of fruit, soft drinks, and confectioneries), or Japanese (high intake of rice, miso soup, sea products, and fish, and low intake of bread, confectioneries, and dairy products) dietary patterns in 763 mother-child pairs found no association between diet during pregnancy and development of AD in offspring at 16 to 24 months.[47] Unfortunately, a longitudinal data analysis has not been performed for this study.

Final Thoughts

Atopic dermatitis is a complex, progressive, and heterogeneous disease with both genetic and environmental influences. Studying the effects of diet on the development, progression, or severity of disease can be very difficult due to the heterogeneity of study designs, lack of long-term follow-up, and high potential for residual confounding. Studies evaluating dietary patterns or supplement intake can be equally challenging, as data often are derived from questionnaires with bias in response to families with higher socioeconomic status.[9] Very few studies have looked specifically at maternal dietary composition and the development of AD alone (without inclusion of asthma or food allergy). Ultimately, the inconsistency of the data makes it difficult to draw conclusions and make formal recommendations for this vulnerable population. Additional evidence from well-powered trials with comparable methodology and objective outcome measures will be imperative to make formal recommendations. In addition, longitudinal follow-up will be essential to determine long-term benefit and influence on the atopic march.

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