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Breastfeeding, the Immune Response, and Long-term Health

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Breastfeeding provides unsurpassed natural nutrition to the newborn and infant. Human breast milk also contains numerous protective factors against infectious disease and may influence immune system development, as noted in previous studies of infant response to vaccination and thymus gland development. If immune system development is significantly improved with the introduction of components of breast milk, then prematurely discontinued breastfeeding may facilitate pathogenesis of many chronic diseases later in life (eg, autoimmune disorders). The authors summarize the reported effects of breastfeeding on the development of the suckling infant's immune system and discuss possible consequences to immunologic health when breastfeeding is discontinued prematurely.

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In addition to being the best source of nutrition for newborns and infants, human breast milk also provides immunologic protection against many infections.[1,2] Although most of the immunologic benefit cited by researchers relates to protection from diarrheal diseases that are especially prevalent in developing countries,[2,3] breastfeeding has also been shown to protect infants against extraintestinal infections, such as otitis media[4–6] and respiratory diseases.[7–10]

Less convincing, but still substantial, is the evidence that suggests breastfeeding can influence immune system development, affecting the pathogenesis of autoimmune disorders, including atopic allergies. This claim is difficult to prove, however, because immune system disregulation is multifactorial in origin and may be asymptomatic for several years after weaning. The early positive influences of human breast milk may be a bulwark against chronic disease in later life.

This review summarizes many of the known immunologic components of human breast milk and examines the evidence for long-term health afforded to breastfed infants. In particular, we will examine the influence of breastfeeding on immune system development and the pathogenesis of chronic disease.

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Immunologic Factors in Human Breast Milk

For the fetus and newborn, immunologic defenses are present, but immature. To compensate, the mother's immunoglobulin (Ig) G antibody moves across the placental barrier to provide some protection. After birth, these maternal antibodies wane in the first 6 to 12 months of human life. The neonate and infant can receive additional maternal protection from breast milk, however.

Human breast milk contains large quantities of secretory Ig A (sIgA). These antibodies, which have formed as a consequence of the mother's previous exposure to infectious agents, can bind to potential pathogens and prevent their attachment to the infant's cells. Secretory IgA is adapted to survive in the respiratory and gastrointestinal mucosal membranes and resist proteolytic digestion. Secretory IgA neutralizes infectious agents while at the same time limiting the damaging effects of tissue inflammation that can occur with other antibody types.

Human breast milk, and especially the early colostrum, contains measurable levels of leukocytes. Colostrum contains approximately 5×10^6 cells per mL, an amount that decreases tenfold in mature milk. Most of these leukocytes are macrophages and neutrophils, which phagocytose microbial pathogens. Lymphocytes, including T cells, natural killer cells, and antibody-producing B cells, make up 10% of the leukocytes in human breast milk. There is evidence to suggest that these cells survive passage through the infant's gastrointestinal system where they are absorbed and influence the infant's immune response.[11] Much of this evidence comes from animal studies, however, which will be discussed later in the present review.

In addition to these immunologic components, breast milk contains several nonspecific factors that have antimicrobial effects.[12] These factors include the enzyme lysozyme, which inhibits the growth of many bacterial species by disrupting the proteoglycan layer of the bacterial cell wall. Lactoferrin, one of the most abundant proteins in human milk, also limits bacterial growth by removing essential iron. Nucleotides in human milk have been shown to enhance immune function in infants.[13] Complex sugars are found only in trace amounts in cow milk but make up a substantial portion of human milk sugars, where they may prevent adherence of various microbial pathogens by acting as decoy receptors.[11]

Obviously, human breast milk contains a wealth of

immunologic and other protective mechanisms that decrease neonatal infections. But, is that the whole story, or are there effects that reach beyond infancy? Do immunologic factors in breast milk influence the development of the infant's immune system to the extent that they influence the pathogenesis of chronic disease later in life?

Breastfeeding and Immune System Development

The thymus is a central organ in the immune system, responsible for the proper development of T lymphocytes. Immature T cells, known as *thymocytes*, undergo a selection process in the thymus to remove potentially self-reactive cells. Less than 5% of thymocytes survive this "education" to be released as functionally mature, circulating T cells. While the clinical significance of thymic size is not known, the central role of the thymus gland in the development of the T-cell repertoire suggests a potential for direct effects of breastfeeding on a crucial organ of the maturing immune system.

Using an ultrasound technique to measure thymic index size, Hasselbalch and colleagues[14] found that, at 4 months of age, infants who were breastfed exclusively had significantly larger thymus glands than those who were partially breastfed or formula fed only. There was no significant difference in thymic size among the three study groups at birth.

A later study by Thompson and coauthors[15] was unable to confirm the findings of Hasselbalch et al[14] by measuring thymic weights at autopsy in infants who died of sudden infant death syndrome.

Prentice and Collinson[16] later tried to reconcile the work of Hasselbalch and Thompson, speculating that in vivo thymic size differs from that found at autopsy because of the inherent plasticity of the organ.

Hasselbalch's group (ie, Jeppesen et al[17]) has recently published a report that not only substantiated their previous findings regarding increased thymus size with breastfeeding, but also found a correlation between breastfeeding and $CD8^+$ T cells.

Breastfeeding and Childhood Vaccination

It has also been suggested that breastfeeding influences an infant's response to common childhood vaccinations.[2,3] Several studies have shown increased immune response to vaccines in breastfed vs formula-fed babies.[18,19] Greenberg and colleagues[20] studied immune responses to *Haemophilus influenzae* type b-tetanus toxoid conjugate vaccine in a subset of 10,000 immunized infants and found a significant increase in antivaccine antibody in infants that had been breastfed for at least 6 months. Other studies[21,22] have found no such positive effects, however. Still others have even found a significant adverse effect on seroconversion.[23]

Studies showing no effect or adverse effects of breastfeeding in childhood vaccinations often used live viral vaccines whose immunogenicity may be inhibited by the sIgA of human breast milk. For example, the three studies included in the meta-analysis by Pichichero,[23] with approximately 500 infants in total, all examined antirotaviral responses after an oral dose of a live attenuated Rotavirus vaccine. Proper immunization with live oral virus vaccines depends upon viral replication, which could be inhibited by the sIgA of breast milk. Indeed, increasing the vaccine dose diminished the "adverse" effect of breastfeeding.[23]

There is some evidence from animal studies and other work to suggest that cells in breast milk survive passage through the intant's digestive tract, are taken up into the gut mucosa, and are found in the draining lymph nodes.[3,24–26] Evidence that these cells remain functional comes from the observation that positive skin responses to injection of the mycobacterial-purified protein derivative can be transferred from one individual to another by breast milk.[27] Other studies[28,29] have shown reductions in the alloreactivity of breastfed infants who were given maternal allografts. This evidence tends to support the idea that breast milk leukocytes are able to survive and interact with the intestinal mucosa of the infant, which could lead to a form of tolerance to maternal antigens.

Allergy, Autoimmunity, and Breastfeeding

Does breastfeeding decrease individuals' future susceptibility to autoimmune disorders? This question has been debated and tested for many years with mixed results.[30–36] In a special report for the *Journal of Pediatrics*, Kramer[30] developed 12 standards of biological and methodological parameters by which studies on breastfeeding and atopic allergies could be evaluated. Kramer[30] applied these standards to studies that were published from 1983 through 1986 and found on MEDLINE. Weaknesses found in many of the studies included reliance on long-term maternal recall data, insufficient data on duration and exclusivity of breastfeeding, and lack of strict diagnostic criteria for atopic allergies. No firm conclusions could be drawn from the analysis.

A recent meta-analysis by Mimouni Bloch and coinvestigators[37] examined studies of breastfeeding and allergic rhinitis published between 1966 and 2000. Prospective studies in which infants were breastfed exclusively for the first 3 months were included in this analysis of six studies. The authors concluded that exclusive breastfeeding during the first 3 months of life protects children against allergic rhinitis. This association was substantial (summary odds ratio of 0.74), but not statistically significant. The authors suggest that this small, though statistically insignificant effect, might result from the strict inclusion criteria for the meta-analysis, which used studies that focused on allergic rhinitis rather than all forms of atopy, and studies that met the strict methodologic criteria proposed by Kramer.[30]

A multicenter group from Northern Europe also conducted a review of the literature related to breastfeeding and atopic allergies and concluded that breastfeeding seems to protect individuals from atopic allergies.[38] This study included data from 56 published articles that were judged to be con-

clusive. Several of these studies gathered follow-up data into subjects' adolescence.

It has been further suggested that breastfeeding facilitates increased immunologic tolerance, and may thus decrease future risk of autoimmune disorder.[24] Koletzko and coauthors[39,40] found that formula feeding in place of breastfeeding was independently associated with increased risk of Crohn's disease but not ulcerative colitis. These studies were conducted using questionnaires sent to families with at least one child (<18 years) who had been diagnosed with inflammatory bowel disease.

In a more recent study, Corrao and colleagues[41] found that formula feeding was associated with an increased risk of Crohn's disease or ulcerative colitis in 819 patients with inflammatory bowel disease. This relationship was statistically significant for Crohn's disease in women. Lack of accurate parental recall on infant feeding methods is a potential weakness in these studies, however.

Insulin-dependent diabetes mellitus (IDDM) is largely a result of genetic factors and disregulation of the immune system. Breastfeeding has been shown to have protective effects,[42–44] no effects,[45–47] and even detrimental effects[48] on the risk of IDDM or diabetes-related auto-antibodies.

In 1994, Gerstein[44] attempted to bring some clarity to this relationship with a critical review of the literature (N=19). Overall, countries with the lowest prevalence of breastfeeding at 3 months of age had the highest rates of IDDM. In case-control studies, patients with IDDM were more likely to have been breastfed for less than 3 months.

Norris and Scott[49] published a meta-analysis of similar studies (in fact 68% of Gerstein's studies were also part of Norris and Scott's analysis) that found a moderate increased risk of IDDM associated with age at first exposure to breastmilk substitutes, which were defined as any milks or foods other than breast milk in the infant diet. These authors discussed the many potential sources of bias in these studies (eg, retrospective assessment of feeding practices, inaccurate recall, and difference in response rates between cases and controls) and concluded that small associations between infant diet and risk of IDDM may be explained by problems in study design that created bias.

In Sweden and Lithuania, a recent case-control study of 803 children (≤15 years) was aimed at determining whether forms of early nutrition were independent risk factors for diabetes.[50] Information was gathered by questionnaires distributed at the time of diagnosis with IDDM. The authors concluded that formula feeding in place of breastfeeding was independently associated with diabetes, after adjusting for other variables.

Conclusions

Disease prevention is critically important to individual and public health. Breastfeeding is well known to provide immune protection and prevent various diseases in the perinatal period. Human breast milk is also accepted as the best nutritional source for the neonate and infant, and it provides other widely accepted benefits to the mother and child. Additionally, there are specific maternal benefits, including the delayed resumption of menses and subsequent reduced risk of anemia, as well as substantial association with bonding and emotional gratification. Indeed, there are even benefits to society overall through reduced child mortality rates, the economic advantages of breastfeeding over formula consumption, and the "environmentally friendly" aspects of lactation. It is estimated that improved breastfeeding practices could save 1 million to 2 million lives per year.[51]

Could early consumption of human breast milk also provide long-term benefits by protecting individuals from chronic diseases later in life? We examined the literature for evidence of long-term benefits of breastfeeding that may influence autoimmunity. While the evidence is not conclusive, there is enough evidence to suggest that breastfeeding may significantly alter the immune system of the suckling infant. Clues to this early influence are seen in the effects of breastfeeding on thymic size, the antibody response to vaccination, and increased tolerance to breast milk leukocyte antigens. Fundamental changes in the infant's immune system as a result of premature cessation of breastfeeding could lay the groundwork for later dysfunction in the immunologic controls necessary to prevent autoimmune disease or hypersensitivity reactions.

Autoimmune disorders are common and affect quality of life for millions of Americans. The incidence rates for some of these diseases have been increasing over the past several decades. Much of this increase can be attributed to increased levels of environmental allergens, pollutants, and lifestyle. The preponderance of evidence suggests that exclusive breastfeeding, for at least the first 6 months of life, can decrease the incidence of atopic allergies. In theory, enhanced maturation of the intestinal mucosal barrier could decrease translocation of protein antigens and thereby decrease unwanted immune stimulation. However, since there are multiple factors involved in allergic disease (eg, genetic history of atopy, environmental exposures), the effect of breastfeeding should be viewed as one word in a very long sentence. Future studies on this relationship should adhere to the standards described by Kramer[30] and should also require researchers to gather information on maternal diet as a possible confounding factor.

Although recent claims point to breastfeeding as preventive of IDDM, the evidence is far from conclusive. The most recent study cited above shows a protective effect.[50] Arguments in favor of the protective effect of breastfeeding include the apparent capacity of breast milk factors to enhance maturation of the intestinal mucosal barrier and, thus, enhance development of oral tolerance.[11] Unfortunately, the numerous confounding variables and potential for bias inherent in most of the study designs used make definitive inferences very difficult. If further research can confirm this protective effect, the implications for proactive interventions could be substantial.

In their early review of breastfeeding, Wold and Adler-

berth[11] commented on the abundant protection provided to the neonate and infant by human breast milk and added that perhaps we should not expect lifelong immunologic protection as well. Even if breastfeeding is later proven to have no effect on the pathogenesis of chronic disease, there are enough short-term benefits from breastfeeding to justify its continued promotion as the exclusive nutritional supply for the newborn.

Osteopathic primary care physicians should promote breastfeeding at every opportunity. The American Academy of Pediatrics has listed specific steps that pediatricians and family physicians should take to promote breastfeeding and support those parents who have decided to breastfeed.[52]

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