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Breastfeeding and risk of parasitic infection-a review

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PEER REVIEW

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Comments

This is an interesting review to describe the association between breastfeeding and risk of parasitic infections and explore the underlying immune responses.
Details on Page 855

ABSTRACT

Breastfeeding, as exclusive nutrition in the first six months of life, is a necessary nutritional requisite in infants. Except for very few maternal diseases that contraindicate breastfeeding, some of which still controversial, breastfeeding mothers must continue exclusive and sustained lactation to provide maximum overall benefits through breastfeeding. Parasitic infections is a global disease and children remain a significant proportion of the affected population. The complex and mandatory life cycles of some parasites, particularly the helminths may partly explain their geographical distribution. The world-wide prevalence of parasitic infections as well as the largely asymptomatic nature of most infections, make many of these infections to likely remain under-recognized. Breast milk, the prime infant nutrition must be recognized to be more than a rare vehicle of parasite transmission, but also a general and focused immune defensive tool against some important parasites. The possibility and influence of small quantities of parasite antigens in breast milk have not been adequately explored. It is believed that useful immunological responses both direct and indirect in breast milk that occur due to the presence of parasite antigens, must be further studied in the light of both immediate and long term benefits. Within this context, and prompted by a spectrum of existing uncertainties, researched and hypothetical roles of parasites and associated immunological responses in the lactating mammary gland are proposed and reviewed.

KEYWORDS

Breastfeeding, Parasites, Infection, Uncertainties, Hypothetical, Mammary gland

1. Introduction

The nutritional consequences of parasitic infections are well recognized in children[1]. Parasites of medical importance include the single cell eukaryotic protozoa, the multicellular eukaryotic helminths, and the arthropod vectors that transmit diseases[2]. The main groups of parasitic helminths include nematohelminths (nematodes) and platyhelminths (flatworms)[2]. Platyhelminths are subdivided into cestodes (tapeworms) and trematodes (flukes) [2]. Geohelminths (soil-transmitted helminths), intestinal parasites causing human disease include the roundworms [*Ascaris lumbricoides* (*A. lumbricoides*)], whipworms [*Trichuris trichiura* (*T. trichiura*)], and two hookworms (*Ancylostoma duodenale* and *Necator americanus*)[3].

In children, parasitic infections acquire their full nutritive capacity from a host that can ill-afford to share and often tips the balance of a precarious nutritional state towards its favour. Malnutrition that ensues encourages parasitic infections to flourish as the malnourished host is incapable of effective immunological responses required to limit or to effectively eliminate such infection[4]. Nutrition is linked

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to immunological processes as nutrition provides necessary substrates for many immunological mediators for important immunological reactions *in vivo*[4]. In children, infections causing prolonged diarrhea predict the development of malnutrition at twelve months of age[5]. Certain parasites in children can cause protein and energy linked nutritional disorders, micronutrient deficiencies and failure to thrive[6].

The mechanisms underlying failure to thrive or inadequate weight gain in children vary according to the type of helminthic infections[3]. Ascariasis causes malabsorption as a result of villous atrophy and lactase deficiency[3]; trichuriasis produces bloody, mucoid diarrhoea and rectal prolapse[3,7]; hook worms interrupt absoprtion of nutrients through ingestion and digestion of host blood producing the hallmark of a microcytic hypochromic anaemia and can cause a systemic suppression of host immunity not only to itself but also to antigens such as vaccines and allergens[8]. In the young, recognized consequences of chronic heavy hookworm infections are also mental deficits such as poor memory and learning difficulties as iron is required in the synthesis of dopaminergic neurons and some metalloenzymes[9].

The feedback loop between nutritional inadequacies, infections and further deterioration of nutrition is a significant contributor to childhood morbidity and mortality in some parts of the world[4]. The concept of good nutritional care must encompass an approach that deals both with the treatment and more importantly, the prevention of these problems. The immune competence of breast milk may confer important protection[4].

Considering the frequency of parasitic infections worldwide, where one billion people are infected with soil-transmitted helminths, and four hundred million children of school age are infected with many other types of gut parasites[4]- the mother who breastfeeds could well harbour low level of parasites in her gut or any organ system the parasite normally resides in or infects; consequently breastfeeding in the presence of maternal parasite infection is a common clinical scenario to encounter. Although such infections rarely produce symptoms, they are much more likely to be entirely asymptomatic. Hence, breastfeeding and asymptomatic maternal parasitic infection and the effects thereof, should be considered in greater detail.

As similar socioeconomic and sociocultural habits of mother, infant and environment usually coexist, it is possible that the breastfed child may also harbour or be infected by similar parasites just as the mother sometime during the child's life[10]. Additionally, the recognized association of parasitic infections with the lack of accepted standards of hygiene accentuated by poverty and sociocultural habits, are risk factors for parasitic infections in early life. The incorrect marketing of complementary foods that could impede breastfeeding or encourage the consumption of nutritionally inadequate foods are concerns[11]. Lack of maternal education and ignorance of proper infant feeding methods potentially propagate parasitic infections in a community[3]. Interestingly, a study revealed that parental illiteracy on the whole was a recognised risk factor for *Giardia duodenalis* infection but went on to highlight that paternal illiteracy, as a more important risk for the infection[12]. The study also revealed a possible link between *Helicobacter pylori* infection and *Giardia* infection[12]. Infection in nurseries and day care centres are known[13]. When an infant is not exclusively breastfed, other contributing factors in preparation of artificial formula or complementary foods can be risk factors for parasitic infections. Contamination of infant feeding by water infected by animal or human excreta, inadequate chlorination of water and person to person feco-oral transmission are risk factors[3,13,14]. Aggravation of this situation by human sociopolitical disasters like refugees and refugee settlements have reported frequent strongyloidosis and other parasitic infections linked to sanitation, poor quality of drinking water and lack of foot wear[15].

Particularly in the absence of breastfeeding, one may be concerned about specific immunosuppressive states. Certain clinical circumstances predispose to unique parasitic problems[16]. Chronic helminth infections affect T cell function and lead to immunosuppression[3,17]. Soil transmitted helminths infections often found in areas, endemic to many other infections, increase the risk of diseases such as tuberculosis, malaria, and HIV[3,18-20].

A number of parasitic infections such as *Opisthorchis viverrini*, *Clonorchis sinensis* and *Schistosoma hematobium* are associated with the development of cancer[21].

Cryptosporidium parvum has been linked to digestive carcinogenesis in humans[22]. In a study of the prevalence of intestinal parasites in immunosuppressed children, more than a third had parasitic infections including *Giardia lamblia* (*G. lamblia*), *Entamoeba coli*, *Blastocystis hominis*, *Iodamoeba butschlii*, *Chilomastics mesnili*, *Hymenolepis nana* and *Enterobius vermicularis*[23].

Considering the overall health impact of parasitic infections, it is useful to know if breast milk can protect against parasites and whether a mother infected with parasites influences the course of the infection or the immunological outcome of the disease in her nursing child.

2. Breastfeeding is advantageous in parasite infections of the young

The American Academy of Pediatrics reaffirms its recommendation of exclusive breastfeeding for 6

months, continued breastfeeding with the introduction of complementary foods, and continuation of breastfeeding thereafter for one year or even longer as desired by mother and infant. The growth of the infant should be monitored with the World Health Organization Growth Curve Standards to avoid mislabelling infants as underweight or failing to thrive[24].

As alluded to earlier, in view of the overall nutritional and immunological impact of parasitic infections in the growing child, it is well to appreciate that there are fundamental differences in the composition of breast milk compared to formula milk contributing to a broad-based immune-nutritive anti-parasitic capacity. The high quality and efficiency of proteins in human milk of a well nourished mother are gold standards in infant feeding[25]. In the whey protein fraction of human milk are α lactabumin, lysozyme, serum albumin, lactoferrin and immunoglobulins[25-27]; some are important for immunological function. Lysozyme and lactoferrin in breast milk contribute to the development of beneficial intestinal microbiota[28]. Breast milk guides the development of a protective intestinal microbiota in the infant. Genomic analysis of bifidobacteria from infants indicates that specific genetic loci are related to milk oligosaccharide suggesting a close evolutionary link between the human host, milk glycans, and the microbes they enrich[29]. All ten essential amino acids are abundant in milk colostrum and form a fairly significant proportion of its total nitrogen content[25]. Optimal nucleotides levels for immune function, growth, gut maturation and enzymatic reactions are best achieved by exclusive breastfeeding[25].There is nutritive proficiency of zinc and iron compared to formula milk and regulation of maternal stores of important micronutrients, where improved bioavailability spares energy for growth and immunological defenses. Bioactive components in human milk are ingredients for maturation of innate and adaptive immunity[25,26]. Bifidobacteria in the gut of the breastfed infant links mode of feeding with physiological homeostasis[30]; where nutrient processing by microbiota and host diet combine to shape many immune responses[31]. The favourable microenvironment in the gut of the breastfed further educate the immature immunological system towards advantageous immune responses[30,31]. Breast milk human alpha-lactalbumin made lethal to tumor cells (HAMLET), a protein-lipid complex formed in the infant's stomach from α-lactalbumin and oleic acid induces apoptosis and sensitises pathogens to antimicrobials and tumor necrosis factor (TNF)-related apoptosis-inducing ligand in breast milk is associated with anti-cancer effects[32-35]. Hence, overall the breastfed infant is better equipped nutritionally, immunologically and possibly in the long term when challenged by parasitic infections (Figure 1).

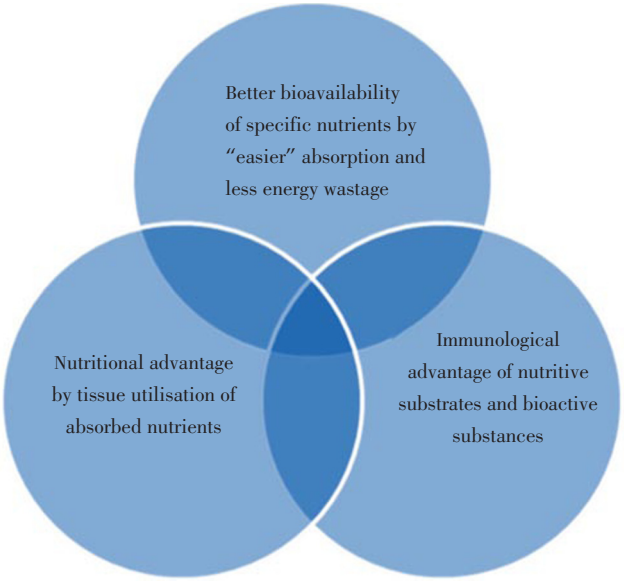

Figure 1. Hypothesis: how breastfeeding can be advantageous to a child with parasitic infection (BIN benefits).

3. Consequences of breastfeeding in maternal parasitic infections-some questions and hypothetical inferences.

The feedback loop of parasitic infections and malnutrition may be interrupted by exclusive breastfeeding. Hence, during most parasitic infections a mother should continue to exclusively breastfeed her infant.

In advising on breastfeeding in a setting of parasitic infections in the mother, it may be deemed useful to ask about: i) the effects of breastfeeding in maternal parasitic infections; ii) parasite influence in breast milk; iii) the general and specific protective factors in breast milk against parasites; iv) gaps in our knowledge about parasites and breastfeeding for further reflection, hypothesis and research.

3.1. In general, is it hazardous to breastfeed in maternal parasitic infections?

Often maternal parasitic infections are asymptomatic. When a mother is found to harbour parasites incidentally or as a result of clinical symptoms, breastfeeding counsellors would benefit to know if breastfeeding can be continued.

It stands to reason that the transmission of whole parasites via breast milk is infrequent given the size of parasites in general, that must cross the 'blood milk barrier' to enter the lactating mammary gland. This barrier consists of mammary gland endothelial and extracellular cells separated by an extracellular matrix[36]. It would be expected that a heavy parasite burden in the mother has to occur before even the smaller parasites attain a level that would allow 'breach' or 'spill' permitting entry into the lactating mammary gland. The decision to disallow breastfeeding is unusual and only few contraindications exist to breastfeeding.

A well studied parasite in association with breastfeeding is *Trypanosoma cruzi* infections. Chagas disease (CD) can be acquired through the ingestion of contaminated food or water. In humans, contamination of milk with trypomastigotes has been described; however, except for some dated and inconclusive cases, transmission through breastfeeding has not been reported[37]. The discontinuation of breastfeeding by mothers with chronic CD is not recommended[37-39]. However, breastfeeding by mothers, with acute CD or with fissures and bleeding nipples, should be avoided[37-39].

Toxoplasmosis may be transmitted by the foetus swallowing amniotic fluid containing infected leukocytes and other cells or by the elimination of *Toxoplasma gondii* (*T. gondii*) in the breast milk during lactation[40]. It is a cause of intrauterine malformations and is a part of the TORCHES syndrome (toxoplasmosis, other agents, rubella, cytomegalovirus, cytomegalovirus, herpes simplex). Although breast milk is debatable as a vehicle of transmission, probable transmission of *T. gondii* tachyzoites in breast milk has been reported[40,41].

Breast milk as a rare vehicle for infantile hookworm infection has been reported where infective larvae of *Ancylostoma duodanale* that have arrested in pregnant women enter postpartum into the colostrum and breast milk[42].

Most parasitic infections in the mother do not contraindicate breastfeeding although it is pivotal that maternal health and nutrition is good and the parasite load is kept to the minimum. Without sufficient support to advice on the contrary, exclusive breastfeeding is adviced in the face of most maternal parasitic infections.

3.2. If the passage of parasites into breast milk is unlikely, do parasitic infections in the mother "enter" or "influence" breast milk ?

There is evidence to support that parasite antigens occur in human milk[43]. The occurance of parasite antigens within the lactating mammary gland is seen in the milk of women affected by a filarial parasite, *Onchocerca volvulus* (*O. volvulus*)[43]. In general, it is known that antigens within breast milk can be a trigger for the immature immune system to respond immunologically[43]. When such filarial antigens are detected, breast milk does not seem primarily a vehicle for transmission of filariasis, instead, as a source that provides an opportunity for the naive immune system to mount relevant protective defences[43,44]. In filiariasis, *O. volvulus*-specific cellular responsiveness and cytokine production in newborns from infected mothers have been noted[44].

Another potential route for immunological reactions is the endogenous link between both maternal and infant immune responses through the enteromammary axis-as a result of immunological mediators in contact with the parasite in the gut of the mother. In such a scenario, maternal parasite antigens provide the first source to stimulate and subsequently trigger antigen specific immunity which is mainly focused towards immunological responses towards the parasite the mother harbours. Breast milk supplies the first source of antigen-specific immune protection in the gastrointestinal tract of the breastfed infant[45]. Secretory immunoglobulin A (sIgA) can also be protective by influencing gut microbes and host expression of genes[45,46].

3.3. General and specific parasite protection in breast milk

The infant relies on innate defenses as essential first line protection. There is suggestion that breastfed infants have earlier recall of innate immune cells compared to formula fed infants[47]. Innate factors that have anti-parasitic activity are present in breast milk[48]. Whether maternal parasite antigens influence innate factors in breast milk either quatitatively or qualitatively is not known. Among human parasites, infection by *G. lamblia* is common and recognized as an important cause of chronic malabsorption and failure to thrive in some parts of the world. The establishment of infection would require parasite attachment to the gut mucosae; while attached to the gastrointestinal epithelium, *Giardia* causes apoptosis of the epithelial cell, interrupts tight junctions, and increases intestinal permeability[49]. Breast milk colostrum controls proliferation and growth of intestinal cells[50]; healing of tissues damaged by epithelial disruption or ulcers can be facilitated by virtue of the abundant growth factors present in colostrum[51] (Figure 2). Anti-*Giardia* factors in breast milk that prevent the establishment of infection or reduce parasite load may act by inhibiting parasite attachment to the intestinal epithelium, by opsonization and phagocytosis of *Giardia* trophozoites[52].

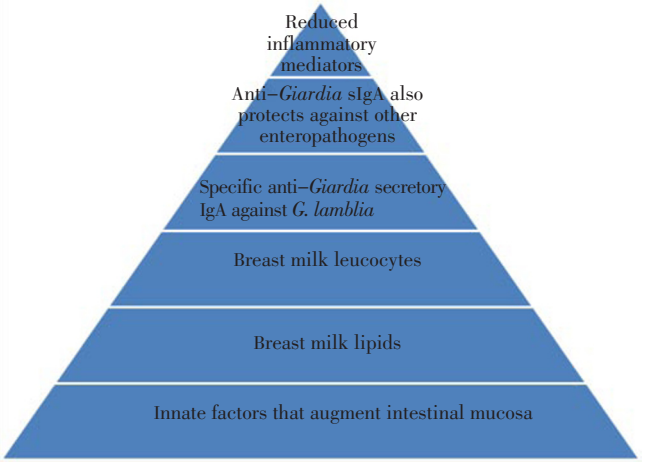

Figure 2. Known and postulated breast milk protection conferred in giardiasis.

Mucosal integrity is a factor of importance in helminthic infections and if impaired, its barrier function is affected. There is increased mucosal permeability and fluid

accumulation within the gut in some geohelminthic infections[53]; this may affect absorption of nutrients. A prospective study of infants in an urban slum showed that in diarrheal diseases where enteric protozoa were important causes of the diarrhea, the development of malnutrition was associated with intestinal barrier disruption and diarrhea was more severe in malnourished children[54]. In that sudy, the protozoans were *Entamoeba histolytica* (*E. histolytica*) and *Cryptosporidium*[54].

A spectrum of intestinal growth factors stimulate growth and strengthen gut mucosal "barriers" as first line defences to infection[55,56]; as well as to parasites that inhabit the gut. Within breast milk, growth factors and cytokines such as epidermal growth factor, nerve growth factor, insulin-like growth factor, TNF-α, transforming growth factor-α, basic fibroblast growth factor, transforming growth factor-β, granulocyte colony-stimulating factor, interleukins: IL-1β, IL-6, IL-8, IL-10, prostaglandin and milk cortisol directly or indirectly influence mucosal integrity of the gastrointestinal tract[55,56]. Innate factors such as breast milk mucin could potentially counter or ameliorate penetrative action by some geohelminths. Gut seepage and impaired epithelial function are pathology seen in roundworms *A. lumbricoides*, whipworms, *T. trichiura*, and hookworms, *Ancylostoma duodenale* and *Necator americanus*[3]. Trefoil factors from mucin producing cells in breast milk function in healing of the gastrointestinal mucosa[57]. These factors activate intestinal epithelial cells, produce defensins and are involved in innate protection in the breastfed infant[57].

In *G. lamblia* infections, the young in developing countries are shielded against symptomatic disease upon exposure to *G. lamblia* by breastfeeding on milk containing high titres of anti-*Giardia* sIgA as a consequence of maternal exposure[58] (Figure 2). This type of passive protection allows the child to acquire active immunity upon exposure to *G. lamblia* without having to suffer clinically overt infection[58]. Innate breast milk factors such as lipases and fatty acids possess activity which includes cytotoxicity of *G. lamblia*[59]. Bile salt stimulated lipase in breast milk is also cytotoxic against *E. histolytica* infections,another globally important cause of parasite induced diarrhea, particularly in developing countries[60]. Epidemiologically, breast-fed infants are at lower risk to acquire *E. histolytica* infections[60]. In one study, *E. histolytica* was found unusually commonly in infants under one year of age who were not exclusively breastfed[61]. Insufficient breast milk had led to the practise of mixed feeding with resultant contamination of water used for bottle feeding (Figure 3). The lack of exclusive breastfeeding resulted in infants less than 1 year presenting with significantly more intolerance to oral feeding, frequent, loose motions, and dehydration as grounds for hospital admission compared to children above one year of age[61].

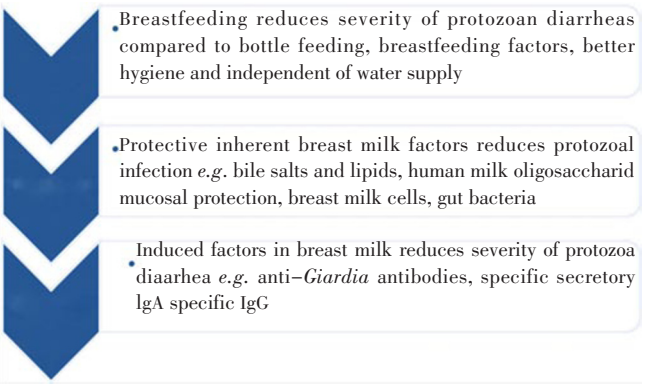

Figure 3. Hypothesis: public health importance of general and specific protection in breast milk against protozoans and helminths.

The cells in breast milk include leucocytes comprised of lymphocytes, neutrophils and macrophages[25,26]. Phagocytosis of *G. lamblia* trophozoites by human colostral leukocytes is a possible an antiparasitic action present in breast milk[52] (Figure 2). Leukocytes in breast milk are involved in protection against E histolytica by cytotoxicity, interfering with both gut colonisation and gut invasion[62]. The actively phagocytic macrophages in breast milk produce lysozyme[62]. Lysozyme induces anti parasitic activity against *E. histolytica*[51]. Additionally, the cytotoxicity of *E. histolytica* is also blocked by human milk oligosaccharides[63]-a dynamic breast milk component[64].

Breast milk contains gangliosides which are acid syphingolipids and vary with the stage of lactation as GD3 is the main ganglioside in colostrum and GM3 in mature milk[65]. These lipids that are associated to the membrane of the milk fat globule have anti parasitic function against *Giardia muris* and possibly *G. lamblia*[65,66]. It is also possible that gangliosides have an effect on enterocyte function[55].

Cathelicidin expressed in breast milk, serves to protect the mammary epithelium during lactation and protects the neonatal gut with a natural antibiotic[67,68]. Lactose in human breast milk induces expression of the cathelicidin gene in colonic epithelium, and acts synergistically with other cathelicidin-inducing factors such as butyrate and phenylbutyrate[68-70]. Although the anti-parasitic activity of human cathelicidin is limited, shorter analogues are able to interfere with the growth and integrity of *E. histolytica* trophozoites[69,71].

Lactoferrin, in breast milk is multifunctional and has a spectrum of anti-parasitic effects against *G. lamblia*, *Plasmodium falciparum*, *T. gondii*, *E. histolytica* and *Eimeria stiedai*[72-75]. Competition for iron between the parasite and lactoferrin is its mechanism of activity against *Pneumocystis carinii*[76]. Lactoferrin has therapeutic properties as it has immune modulatory action and is linked to the potential benefits of causing regression of some diseases[77].

Persistent diarrhea in children has many causes -parasitic

causes include *G. lamblia*, *Cryptosporidium* spp., *E. histolytica*, *Entamoeba dispar* and *Blastocystis* sp[78]. Persistence of symptoms in the gastrointestinal can be caused by an inflammatory colitis. Cytokines and IgE are found to be elevated in these children[78]. On the whole, TNF-α is elevated in the gastrointestinal tract in cryptosporidiosis, *E. histolytica*-related diarrhea, and giardiasis but serum levels of TNF-α in breast-fed infants are significantly lower than that in the non-breast-fed group with the same intensity of parasite infections[78]; illustrative of an attenuating effect of breastfeeding in these parasite induced diarrheas. Hence, alluding to the protection in breastmilk , it may be postulated that in some parasitic diarrheas, such as caused by G lamblia, the exclusively breastfed infant may have reduced incidence, intensity , duration and other inflammation linked manifestations (Figure 4).

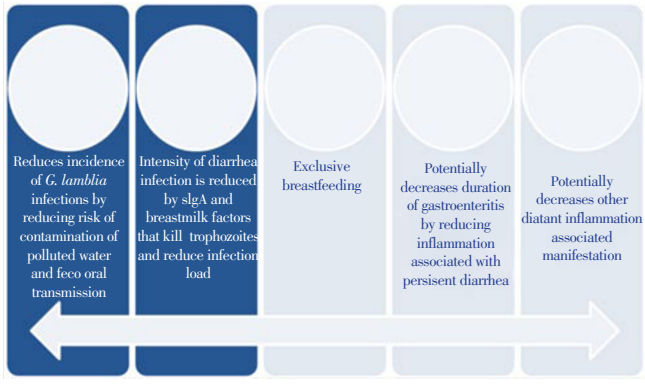

Figure 4. The suggested public health importance of breastfeeding contributing to incidence and intensity of *G. lamblia* infection.

In breastfed infants "good bacteria" of the gut are important in determining the "direction" of maturation of immunity. Together with other maternal and infant factors, the breastfed infant's mucosal and systemic immune responses are influenced by a different micro eco milieu of the gut compared to the formula fed infant. An environment that does not encourage the hatching of *Trichuris trichuria* eggs[79], due to the absence of the required 'pro hatching' bacteria, *Escherechia coli* in the gut in the breastfed, is deemed another indirect anti-parasitic potential that lies within breast milk.

While parasite antigens occur in breast milk and anti-parasitic factors are innately present within breast milk, the passage of parasite antigens in breast milk also seem to induce more specific immune responses. The adaptive arm of breast milk immunity against parasites is induced by maternal exposure or maternal disease. The role of these antibodies in breast milk are not uniform in all populations. An earlier study did not support the concept that there is protection from *Cryptosporidium* infection to children whose mothers have demonstrable breast milk antibodies against the parasite[80]; whereas a later study indicated that the presence of parasite-specific immunoglobulin A in breast milk was associated with protection of infants from cryptosporidiosis[81].

Specific parasite antibodies found in breast milk may originate from maternal blood or from specific mucosal immunity against the parasite[81].

Malaria in young infants may be asymptomatic and often poses diagnostic difficulty, mimmicking sepsis[75]. Although the overall malaria mortality in infants aged under six months is highly uncertain[75], neonatal malaria is thought to be rare[75]: owing to transplacentally tranferred immunoglobulin G[75,82]. Haemoglobin F, present in high concentrations at birth[83], can inhibit parasite development[83], and can protect the infant in the first few months of life. Breastfeeding may contribute to protection by its components such as lactoferrin which binds iron, requisite for parasite survival, and sIgA, found in breast milk and in maternal and infant sera[84]. Additionally, the metabolic substrate para-aminobenzoic acid, which is present only in low levels in breast milk is required for the replication of the parasite[84]. A positive correlation of sIgA both in serum and in the milk of purpurea is reflective of the origin of breast milk antibodies against some parasites[84].Specifically, the presence of significant antibody titers to ring, trophozoite, schizont and gametocyte stages of *Plasmodium falciparum* in breast milk may contribute to protection from this important cause of mortality in some countries[84]. In the light of long term benefits of breastfeeding[85], could this protection from malaria, transferred from mother to infant last beyond the period of suckling?

As part of the mucosa associated lymphoid tissue the lactating mammary gland responds by adaptive or innate factors to specific antigenic stimulation of the gut[86]. Specific breast milk sIgA against *E. histolytica* and *Cryptosporidium* spp., reflect this[81]. Importantly and uniquely, when parasites affect sites other than the gut, the breastfed child can also be protected, anti-parasitic protection at "distant" sites produced by virtue of breastfeeding inhibits *Acanthamoeba*, induced ocular cytopathic effects[87].

Breast milk mucosal immunity potentially also exhibits a wider spectrum of protection than merely towards the parasite- this is suggested by defenses towards other pathogens that can sometimes coexist with parasitic infections[58]. The development of sIgA to *Giardia* may also serve general protection against other enteropathogens[58] (Figure 2); reiterating breastfeeding as an important public health tool in the general prevention of enteric diarrheas.

Parasite endemicity stimulates specific systemic and mucosal antibody responses. A parasite commoner in more unusual human circumstances is *Strongyloides stercoralis* where in endemic areas antibodies against it are acquired

as a consequence of infection. Specific immunoglobulin G and immunoglobulin A both in serum and milk indicate "enhancement of specific mucosal immunity against the parasite "[88] (Figure 3).

Immunoglobulin E influences parasitic infections in two ways. Significant inflammation which can accompany parasitic diarrheas is mediated by immunoglobulin E[78]. Immunoglobulin E responses also activate platelets and induces cytotoxicity against many parasites[78]. In cryptosporidiosis and giardiasis, an elevation in total immunoglobulin E is noted[78]. Excretory and secretory proteins from the parasite *Giardia intestinalis* stimulate production of a specific immunoglobulin E[78]. It is of note that less parasite induced inflammatory responses occur in the breastfed infant as deduced from secretory immunoglobulin E levels. Overall, a protective mechanism present within breast milk (Figure 2).

3.4. Are there gaps in our knowledge about parasites and breastfeeding that require reflection, hypothesis and further studies?

Parasite antigen- antibody responses whether in blood or in breast milk have parasite protective functions. A comparative lesson in blood when extrapolated from Koch's key observation in malaria offers an argument for hypothesis[89]. Exposure to malaria produces species specific immunity - a lower morbidity in older people due to malaria compared to children indicating reduced infectivity in malaria endemic areas. Koch (1900) described "preminution" with a high degree of immune responsiveness with relatively low parasite densities[89]. In malaria, "the dominant factor driving protection from disease may be specific to effectors that diminish parasite numbers, but other effectors such as responses that diminish proinflammatory cytokines, may also play a role"[90]. Our current understanding of infectious diseases indicates that such "preformed" immunity or immunity achieved against the infecting antigen protects against many infections. Similarly, the passage of placental or breast milk protective factors may partially explain why breastfed neonates very rarely get malaria. Drawing from this, exclusive breastfeeding, by its very nature, maybe taken advantage of as a means of "educating" the infant immune system by "consistent and repeated introduction" of parasite antigens to the developing immune system. Innate factors, such as enhancement of mucosal barriers, lactoferrin, anti inflammatory cytokines as well as the adaptive responses are dual resources from which a multitude of defensive factors emerge against parasites in breast milk.

Parasite antigens are responsible for " immune tolerance" or "suppression"[43,91]. Geohelminth infections may negatively impact vaccine immunity in children, by immune suppression[92]. The occurance of immunetolerance or direct antigen induced suppression of immune cells within the breast milk compartment is suggested by parasite antigens in the breast milk of women affected by *O. volvulus* and by subsequent trigger of immune suppressor cells[43].

Could specific parasite-induced responses function for reasons other than those that are directly parasite-related? Specific extracts of helminths or their excretory or secretory products modulate the immune response of the host[93]. The importance of early exposure in determining immune responses have been recognised wherein the exposure to helminth parasites form a pivotal component of the "immune education" to the developing immune system[94]. Can this exposure be extrapolated to breast milk received by the suckling infant whose mother harbours parasites?

Immunologically, it is recognized that parasite-induced responses attempt to counter the parasite as well as have some influence on specific human allergies. As an example, the T helper-2 immune response, resulting in eosinophilia and immunoglobulin E production, characterises both allergy as well as infection induced by helminths[95,96]. As a protective response against parasites, anti-parasite immunoglobulin E is linked to helminthic immunity[95,97]. Hence, it is possible that immunoglobulin E and its receptors evolved as tools to defend against metazoan parasites[95]. Geohelminthic infections such as *A. lumbricoides*, *T. trichiura*, hookworm, and *Strongyloides stercoralis*, are common infectious diseases of childhood in tropical regions where it is observed that childhood symptoms specifically linked to asthma associated with atopy are significantly reduced[98]. Another observation is that early and heavy exposures to *T. trichiura* protect against allergen skin test reactivity later in childhood independent of later infections[99]. Exposure to *T. gondii* or harbouring *Schistosoma* or intestinal helminths reduces the incidence of allergies as parasite antigens are hypothesized to attenuate immune responses and which have an underlying hypersensitive or inflammatory component[100].

In breast milk too there is a spectrum of immune-modulatory compounds. These include nucleotides, polyunsaturated fatty acid, monoglycerides, leuric acid, linoleic acid, specific amino acids, immunoglobulins (sIgA), soluble receptors (CD14, sTLR2), cytokines and chemokines[26,27,101]. Apart from this, bacterial DNA, transferred from the intestines of the mother to the mammary gland through the entero mammary route has an immune modulatory role[102]. Additionally, microRNAs present in breast milk are exosomes, membrane vesicles, that control target gene expression[103]. These microRNA exosomes may be transferred into the infant body via the digestive tract[102]. Hence, besides sexual reproduction, breast milk

acts as a vehicle to transfer genetic material from human to human with potential to transfer immune cells to impact the development of an infant's immune system[104]. Additionally, the extent of breast milk immunomodulation must be appreciated in the light of the potential of breast milk to modulate genetic expression without altering the nucleotide sequence of DNA, favourably influencing diseases even when genetically predisposed[105].

As alluded to earlier both anti-inflammatory responses and immune modulatory responses are inherently present in breast milk uninfluenced by the presence of parasite antigens in the lactating mammary gland. When both parasite immunomodulation and breast milk immune modulation occur, what are the possible effects (Figure 5)? Postulation allows that immune modulation present in both may interact symbiotically, additively or even synergistically, thus shaping immunity transmitted from mother to infant (Figures 6 and 7). The benefits accrued to breastfed children of allergic mothers in attaining systemic allergen specific IgG1 sufficient to inhibit allergic sensitization, is a case in point[106]. Could a mother in a developing country pass on augmented anti-allergic and anti-inflammatory signals in her breast milk as a result of a greater exposure to parasites (Figure 7)? If this is the case, the hygiene hypothesis is "functional" by breastfeeding.

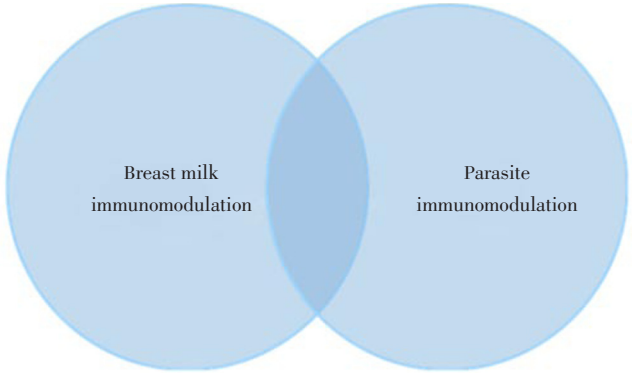

Figure 5. The hypothesised region of overlap requires exploration. The interaction of breastmilk immunomodulation and parasite-mediated immunomodulation may be beneficial.

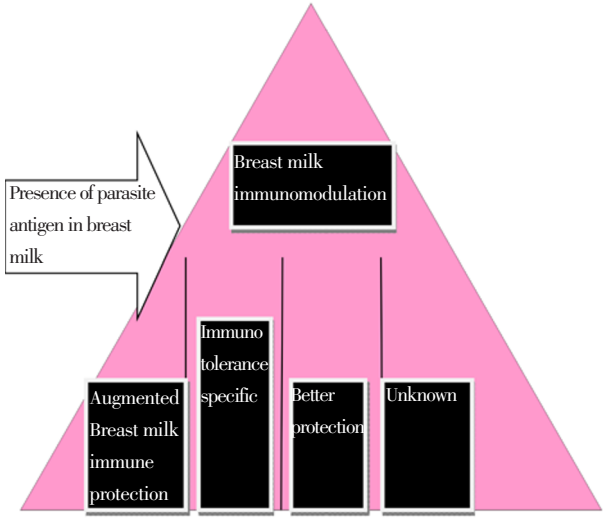

Figure 6. Postulation: how parasites can influence breast milk immunomodulation?

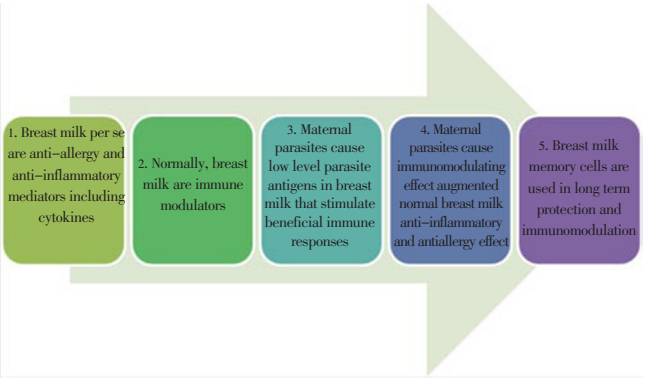

Figure 7. "Symbiotic" action of ingredients in breast milk: a hypothesis-breast milk per se and breast milk with parasitic antigens as a tool to enhance immunity, reduce allergy and unnecessary inflammatory responses.

4. Discussion

A mother who breastfeeds must be nutritionally adequate, hence a significant parasitic infection in the mother cannot exist with successful breastfeeding (Figure 8). Asymptomatic parasitic infections are common in the adult and as discussed, most parasites are not transmitted via breast milk to the suckling infant. On the other hand, it is argued that the passage of low levels of parasite products into the breast milk of mothers may occur in certain parasitic infections and that this can be of immune benefit to the suckling infant. Innate and adaptive factors in breast milk are triggered to partake in non-specific and specific immunity. The avenues of general innate protection in breast milk that augment early defences of the vulnerable intestinal barrier in the infant also seem to have parasite protective features and may reveal something more of the evolution of breast milk immune protection. While the anti-inflammatory and anti-allergic properties of breast milk per se are recognized, it is hypothesised that extrapolation of the hygiene hypothesis to the lactating mammary gland may partly account for the lack of concensus on the verdict of anti-allergic and anti-inflammatory responses obtained by breastfeeding in different parts of the world. Differences in maternal parasitic exposure and, consequently, parasite-induced immunological responses in breast milk that are transmitted to the nursing infant, may contribute to the different levels of protection observed. Certainly, much work needs to be done for elucidation. If breast milk immunology could be influenced by maternal parasites, it may be worthwhile to deliberate on "leaving a few harmless" parasites in the woman of childbearing age or in relevant clinical situations where such enhanced protection may be of benefit to the nursing infant. Hence, a postulated tool in breast milk immunology for modulation of its immunoprotection in its universal role for primary disease prevention.

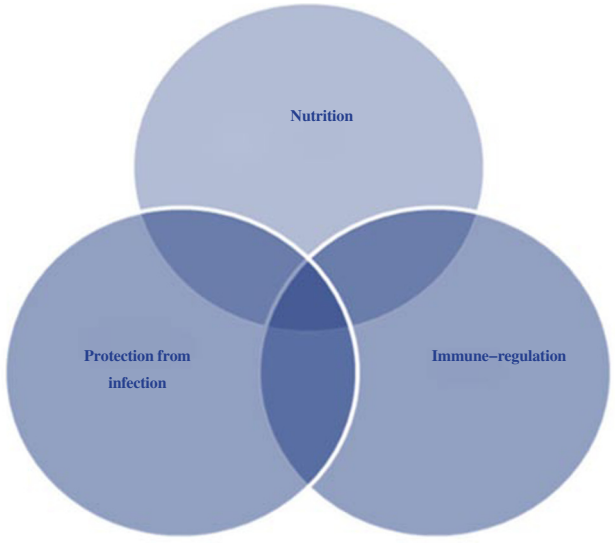

Figure 8. PIN benefits of breastfeeding in the presence of maternal parasite antigens in breast milk-enhanced advantages of nutrition, immuneregulation and protection from infection.

Conflict of interest statement

I declare that I have no conflict of interest.

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Comments

Background

As a necessary nutritional requisite in infants, breast milk is recognized to be more than a rare vehicle of parasite transmission, but also as being an immunodefensive tool against some important parasites. A review to evaluate the association of breastfeeding and risk of parasitic infections and explore the underlying immune responses is needed.

Research frontiers

This review describes the roles of parasites and associated immunological responses in the lactating mammary gland.

Related reports

There have been reviews regarding breastfeeding and CD published previously.

Innovations and breakthroughs

The authors propose "leaving a few harmless" parasites in the woman of childbearing age or the breastfeeding mother. This could well augment breastmilk as a tool in the primary prevention of diseases.

Applications

From the conclusion of this review, the readers will recheck the roles of parasitic infections in the prevention of diseases among women of childbearing age or the breastfeeding mother.

Peer review

This is an interesting review to describe the association between breastfeeding and risk of parasitic infections and explore the underlying immune responses.

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