LITERATURE REVIEW Open Access

Peran Prebiotik pada Gangguan Sistem Imun Bayi Prematur: Sebuah Tinjauan Pustaka Naratif

The Roles of Prebiotics on Impaired Immune System in Preterm Infants: A Narrative Literature Review

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ABSTRAK

Latar Belakang: *Pascakelahiran, bayi prematur menghadapi sejumlah tantangan jangka pendek dan jangka panjang untuk bertahan hidup, tumbuh, dan berkembang dengan sistem kekebalan dan pencernaan yang belum sempurna. Pada 184 negara, laju kelahiran prematur berada pada rentang 5-18% dari seluruh bayi, dan menyebabkan 35% dari seluruh kematian bayi baru lahir.*

Tujuan: *Tinjauan pustaka ini akan merangkum berbagai bukti dampak prematuritas pada perkembangan sistem imun serta manfaat prebiotik pada mikrobiota usus dan respons kekebalan.*

Ulasan: *Berbagai penelitian dalam tinjauan pustaka naratif ini menunjukkan bahwa bayi prematur memiliki kekurangan respons kekebalan secara kualitatif dan kuantitatif dibandingkan dengan bayi yang cukup bulan. Bayi baru lahir prematur juga memiliki gangguan kekebalan pencernaan, penghalang mukosa usus yang belum berkembang, dan disbiosis usus yang meningkatkan risiko mereka terhadap infeksi yang mengancam jiwa. Mikrobiota usus yang seimbang sejak dini pada bayi dapat membantu fungsi fisiologis usus yang memadai dan pematangan sistem kekebalan. Penggunaan prebiotik, termasuk oligosakarida pada air susu ibu (ASI), terbukti dapat menurunkan risiko berbagai infeksi dan gangguan kognitif. Penelitian terdahulu menemukan bahwa suplementasi oligosakarida prebiotik dapat ditoleransi dengan baik, meningkatkan pertumbuhan Bifidobacteria secara signifikan, dan mengurangi keberadaan pathogen usus.*

Kesimpulan: *Terdapat bukti kuat bahwa pemberian ASI dan suplementasi prebiotik dapat mendukung mikrobiota usus dan sistem kekebalan pada bayi prematur. Namun, jenis probiotik sintetik yang berbeda menawarkan manfaat yang berbeda, dan efek perlindungannya bergantung pada dosis dan durasi suplementasi.*

Kata kunci: *Bayi Prematur, Kekebalan, Mikrobiota Usus, Prebiotik, Gizi*

ABSTRACT

Background: After birth, preterm infants face numerous challenges, including short and long-term morbidities, to survive and grow well with impaired immune and gastrointestinal systems. According to data from 184 countries, preterm birth rate ranges from 5-18%, accounting for 35% of all new born deaths.

Purpose: This literature review aimed to summarize the evidence for the impact of prematurity on immune system development and the benefit of prebiotics on gut microbiota and immune responses.

Discussion: Various studies in this narrative literature review showed that preterm infants have both qualitative and quantitative immune response deficits compared to term infants. Preterm newborns also have impaired intestinal immunity, underdeveloped intestinal mucosa barrier, and gut dysbiosis, which predisposes them to life-threatening infections. Early balanced gut microbiota in infants believed to be essential for adequate intestinal physiological functions and immune system maturation. The use of prebiotics, including human milk oligosaccharides (HMOs) in human breast milk, has been found to decrease the risk of various infections and cognitive impairment. A previous study found that prebiotic oligosaccharides supplementation was well-tolerated, significantly increased *Bifidobacteria* growth, and reduced the presence of gut pathogens.

Conclusions: There was robust evidence that breast milk and prebiotics supplementation may support the gut microbiome and immune system in preterm infants. However, different types of synthetic prebiotics offer different benefits, and the protective effect seems to depend on the supplementation duration and dosage.

Keywords: Preterm Infants, Immunity, Gut Microbiota, Prebiotics, Nutrition

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INTRODUCTION

Preterm infants are babies born before 37 weeks of pregnancy. They are grouped into three sub-categories based on the gestational age: extremely preterm (less than 28 weeks); very preterm (28 to 32 weeks); and moderate to late preterm (32 to 37 weeks)[1].

Preterm new-borns have multiple immature systems, which are not helping them in surviving a world full of challenges. According to data from 184 countries, preterm birth rate ranges from 5-18%, comprising 35% of all new born deaths [1,2]. Preterm infants are highly susceptible to infections, such as early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS) and necrotizing enterocolitis (NEC)[2, 3].

One of the significant causes of sepsis and high mortality rates in premature infants is their immature immune system, which affects both the innate and adaptive immune system[4,5]. The immature immune response in preterm infants impairs their defense against infections, especially nosocomial infections that are more frequently found in preterm newborns who often had extended hospital stays[2]. Additionally, the use of invasive procedures, such as catheters, tracheal cannulas, gastric or gastroduodenal tube, parenteral nutrition, and antibiotics in the NICU often interfere with the body's protective skin and mucosal barriers that expose preterm infants to infection[6,7].

Evidence showed that infants' immune system maturation is influenced by their gut microbiota. Early balanced gut microbiota may provide adequate nutrients for their body, positively influence their immune system, and protect them against acute and chronic diseases[8]. There are four main bacterial phyla in healthy infant gut: *Firmicutes*, *Proteobacteria*, *Actinobacteria*, and *Bacteroidetes*. However, preterm infants have lower microbial diversity, disrupted microbiota, and increasing colonization of hospital-acquired potentially pathogenic microbiome compared to full-term infants[3]. Preterm infants have increased *Enterococcus*, *Enterobacter*, *Lactobacillus*, *Staphylococcus*, and decreased *Bacteroides*, *Bifidobacterium*, and *Atopobium*[9].

The disrupted gut microbiota balance in preterm infants can be optimized through prebiotic and probiotic supplementation. Prebiotics are dietary supplements that provide a nutrient substrate to stimulate the growth of health-promoting gut microbiota, while probiotics contain live bacteria. Both supplements have been known to decrease mortality and length of hospital stay in preterm infants[10,11].

The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) stated that there are limitations in probiotic-related studies and pointed out that probiotic efficacy may vary widely according to the strain. Today, the preferred probiotic strain or combination of strains and the optimum dose remain questionable [12,13].

One alternative to optimize the gut microbiota balance is through prebiotic supplementation in the early years of life, primarily with human milk as the most accessible source of prebiotics. Human milk support specific potentially health-promoting microorganisms such as *Bifidobacterium* and *Bacteroides* [5,13,14]. A recent study in Indonesia found that preterm human milk has a different composition than the full-term milk, with the fat concentration and calories that increases with time, and protein concentration decreases with time. The macronutrient content of breast milk for very premature and very low birth weight infants do not meet the recommended needs in those groups[15]. Preterm milks also have a high variety of prebiotic (human milk oligosaccharides) contents[16]. Thus, preterm infants may need additional prebiotic supplementation to support their gut microbiota. However, various research in recent years used different methods of supplementation from human milk to synthetic prebiotics and documented various immediate and long-term effects on infants' growth and development. Therefore, this literature review aims to summarize the pieces of evidence to provide a big picture about the benefits of prebiotics to immune system development in preterm newborns.

DISCUSSION

Impaired Immune System Development in Preterm Infants

The development of fetal immune system begins at 4.5-6 weeks of pregnancy. The process happens in two major categories: the nonspecific innate immune system and the adaptive immune system. Various studies show that preterm infants have both qualitative and quantitative immune response deficits compared to term infants[4]. They are reported to have dysfunction of inflammatory response regulation compared with term infants, including (1) lower circulating T cells concentration, a higher naïve T cells proportion, and smaller storage of neutrophil and monocyte in the bone marrow; (2) lower functional capacity of immune cells; and (3) lower immunoactivity in proteins and cytokines production when provoked [2,5].

The front line of defense against pathogens is the innate immune system that consists of many layers such as skin, mucosal, and chemical barriers, cellular components (monocytes, neutrophils, macrophages, granulocytes, natural killer cells, and dendritic cells), toll-like receptors (TLR), and humoral components (complement system proteins, acute phase proteins, and cytokines). The primary innate immune response involves TLRs that are useful for recognizing pathogen-associated molecular patterns (PAMP) [4,17]. TLR cytokine

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responses are weakened in preterm cord blood compared to term infants[7]. In preterm infants, there is a decrease in antimicrobial proteins and peptides (APPs) production and classical (C1, C4), alternative (factor B), and lectin complement pathways[2].

While the innate immune system can operate effectively without previous exposure to external microorganisms, the adaptive system needs to develop specificity and memory during early childhood. The adaptive immune system is still immature at birth due to limited exposure to antigens during pregnancy and impaired B and T cell function[4]. This condition causes deficiencies in the activation and production of T cell cytokines and B cell immunoglobulins and the interactions between B and T cells[2,17].

Cellular immunity involves T helper lymphocytes (Th; CD4+) and cytotoxic T lymphocytes (CTL; CD8+). When major histocompatibility complex (MHC) class-II is exposed to their T cell receptor (TCR) by an antigen-presenting cell (APC) such as macrophages and dendritic cells, they immediately recognize the pathogens. CTLs are activated by MHC class I and have a role in pathogen eradication. MHC class II activates T helper cells, which are then divided into Th1 (inflammatory) and Th2 (anti-inflammatory) cells according to their cytokine profile. In pregnancy, the cytokine responses are dominated by the Th2 to prevent the rejection of fetus by the maternal immune system, a process that involves the Th1 cytokine production. After birth, the balance between the Th2 and Th1 cytokine responses must be maintained by the regulatory T cells (Tregs) [2,18.]

The humoral immune responses involve B cells recognizing pathogens through antibodies, such as IgM, IgG, IgA, and IgE. Naïve B cells express IgM and IgD, and once activated, will switch their class to lose IgD expression and express another antibody isotype. In infants, this ability is reduced, which causes the B cells to secrete mainly IgM antibodies[2]. The characteristics of expressed IgG and IgA in preterm infants are similar to fetal characteristics. In response to vaccination, they also produce a smaller number of antibodies with lower antigen affinity. Moreover, preterm newborns tend to have slower antibody expression diversification compared to term newborns. The development of antibodies parallels T cell receptors' diversification along with a shift from Th2 dominance toward a Th1 dominance[19].

Since the adaptive immune response is immature, newborns rely on their innate immunity and maternal antibodies to protect themselves from infections[4]. The placental transfer of maternal antigen-specific immunoglobulin (IgG) occurs primarily after 32 weeks of gestation and increases with fetal age[2]. While preparing for postnatal immune defense, fetal immunity also adapts to tolerate maternal antigens in the third trimester of pregnancy[19]. Premature birth interrupts this process, leading to low circulating maternal IgG levels in newborns and phagocytosis deficiencies, and precociously exposes the infant to harmful or protective extrauterine factors such as nutritional antigen and bacteria[2,19]. These events will increase the risk of infection in preterm newborns.

In preterm newborns, intestinal immunity is also impaired. It consists of innate components (gastric acid, intestinal mucin, permeability, protolithic enzymes, defensins, lectins, and cathelicidins) and active immunity (T and B lymphocytes and secretory IgA). IgA protects infants from various pathogens by neutralizing and blocking toxin attachment and penetration. In preterm infants, the secretory IgA (sIgA) levels are lower compared to term infants[4,17]. Underdeveloped intestinal mucosa barrier and gut dysbiosis further predispose preterm infants to severe infections, such as NEC, sepsis, and diarrhea[8,20].

Factors Associated with Altered Immune Responses

Preterm birth is caused mainly by inflammation in the uterus, either due to bacterial infection from the birth canal, placenta, or the amniotic cavity during amniocentesis. It is inversely correlated with gestational age and occurs in about 30% of infants born at ≤ 34 weeks. Prenatal exposure to inflammation may also increase the risk of bronchopulmonary dysplasia (BPD) in infants[2]. Maternal dysbiosis, either in vaginal, fecal, or oral microbiota, may cause inflammation and increase preterm birth risk[8]. Intrauterine inflammation exposure increases the Th1 responses in fetuses, resulting in membrane rupture. It also increases the production of the Th1 cytokines, such as IFN-γ, TNF-α, IL-1β, and prostaglandins, that play a role in typical term labor[2]. It is thought that intrauterine colonization can trigger sensitization or immune activation, causing immune mediators' production and affecting the brain, gut, and fetal immune system[3].

Intrauterine stress conditions due to obstetric and sociodemographic risk factors, nutritional abnormalities, and antenatal hospitalization may increase preterm birth risk. Preterm infants experiencing early-life stress from medical procedures are susceptible to a long-term disfunction of immune responses, including adult persistent inflammation[19]. The birth method influences microbial colonization and gastrointestinal flora of infants at birth, which affects the immune system's development. Babies born through the vagina will acquire microbiota from the vagina. The microbiota facilitates immune precursors' activation in the newborn guts, consisting of the Tregs and Th17 precursors. Both Tregs and Th17 help maintain the balance between Th1 and Th2 responses. Infants born through Cesarean section are known to have a lower gut microbiota diversity at three days of age compared to those delivered vaginally, thus increasing the risk of allergies and other immunity disorders. Infants' TLR-2 and -4 expression are decreased in those delivered by Cesarean section, resulting in reduced responsiveness to bacteria and viruses[2].

The immune system also needs support from micronutrients, such as vitamins A, B6, B12, C, D, E, folate, zinc, copper, iron, and selenium. The lack of dietary micronutrient intakes in specific populations and increasing requirements due to stress or infection may further decrease micronutrients storage within the body. Micronutrients with the most substantial evidence to support immune function are vitamin C, vitamin D and zinc[21].

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Immediate and Long-Term Effects of Altered Immune Responses

Altered innate immune responses may cause common and severe complications in preterm infants, such as BPD and NEC. These inflammation-related risks are further increased by oxidative stress from supplemental oxygen, mechanical ventilation, and intravenous nutrition. Immature anti-oxidant defenses likely exacerbate oxidative stress in preterm newborns 7.

Recent studies have highlighted the association between preterm birth and long-term impacts on immunity, resulting in chronic inflammatory diseases[7]. A meta-analysis involving 31 birth cohorts found that preterm birth was associated with an increased risk for school-age asthma and wheezing. In preterm infants, bronchial hyperreactivity is thought to occur due to different pathophysiological mechanisms from the mechanisms involved in atopic asthma. Preterm infants often have certain risk factors for the development of asthma, such as antibiotic use, Cesarean delivery, and viral infections[19].

Cesarean delivery has been found to increase the risk of adulthood obesity, which is also related to gut dysbiosis that potentially mediates asthma, not to mention being an asthma risk factor in and of itself. Rhinovirus and respiratory syncytial virus are also associated with an increased risk of frequent asthma and wheezing. Bronchopulmonary dysplasia, a pulmonary inflammatory disease occurring most often in preterm infants, may further cause bronchial hyperreactivity, fibrosis, and altered microbiota[19].

Roles of Prebiotics in Immunity Development

Premature infants have an immature digestive system, where their intestinal mucosa barrier tend to be underdeveloped. Pathogenic bacteria and their toxins can easily penetrate the barrier and circulate in the blood and lymph, resulting in severe infections, such as NEC, sepsis, and diarrhea[20].

Early balanced gut microbiota in infants is essential for adequate intestinal physiological functions and immune system maturation. Evidence showed that while the gut microbiota competes with the host's body for nutrients, influences the host's innate and adaptive immune system, and triggers diseases both acute and chronic, they may also be able to generate nutrients for the body, provide a positive influence for the host's immune systems, and protect against acute and chronic diseases[8]. The gut colonization contributes to the development of intestinal motility, and plays a role homeostasis and mucosal barrier function[9]. These functions, along with the interactions between the immune system and gut microbes, are essential for preterm infants to survive.

Various factors are influencing the initial colonization and maturation of the gut microbiota: (1) environmental factors (vaginal vs. Caesarean birth), feeding methods (human milk vs. formula), and microbiota in the NICU; (2) endogenous factors, such as the gut maturation, intrauterine inflammation, maternal stress; and (3) the early use of antibiotics, antiseptics, and infant formula[8]. Main factors that lead to gut dysbiosis are lack of human milk, delayed enteral feeding introduction, and excessive antibiotic use in the NICU[20].

Indonesia has implemented the national program to improve exclusive breastfeeding in health care services, and human milk remains superior to formula in terms of safety, cost-effectiveness, and immunological support. Through their 2016 guideline, the Indonesian Pediatric Society also recommends human milk as the main source of nutrition for preterm infants to provide better immunity, gastrointestinal function maturation, and bioactive factors. However, the exclusive breastfeeding rates remain low, mainly due to concerns in women that they produced insufficient breast milk and the high variability of human milk composition[15,22,23,24].

Prebiotics are non-digestible nutrient substrates that stimulate the growth of health-promoting gut microbiomes, such as Bifidobacteria and Lactobacilli[8,25]. Prebiotic supplementation has garnered much attention in recent years to promote infants' growth and development and prevent morbidities. It may facilitate the probiotic bacteria growth and proliferation in the gut, prevent pathogens' overgrowth, and promote intestinal mucosa maturation. Administration of prebiotics has been known to decrease sepsis and mortality incidences and length of hospital stay[20].

Prebiotics has also been proven to improve preterm neonates' gastrointestinal motility, although the exact mechanism is unclear. Prebiotics appear to modulate gut hormone secretion, such as gastrin and motilin, and reduce lipids in preterm infants[26].

The cheapest and most accessible source of prebiotics is human milk oligosaccharides (HMOs) in human milk. Robust evidence has shown that human milk feeding in preterm infants can prevent NEC, sepsis, retinopathy of prematurity, and cognitive impairment. It may also protect preterm newborns from allergies, autoimmune diseases, and chronic noncommunicable diseases in adulthood[5,27,28,29.] HMOs also block the adhesion of many pathogens to the host mucosal surfaces and act as signaling molecules for cell responses[14].

These HMOs can be utilized as a source of nutrition by only a limited number of bacteria, predominantly Bifidobacterium and Bacteroides[8]. HMOs consumed by breastfed infants support specific microbes with potential benefits for health, including *B. longum* ssp *infantis* (ATCC 15697) and *B. breve* (e.g., SC154, SC95, SC568, and ATCC 15701)[14].

Human milk has been crucial in establishing the intestinal microbiota, with Bifidobacterium dominates the microbial group in breastfed infants. There is a high specialization of infant bifidobacterial species due to oligosaccharides in human milk, primarily *Bifidobacterium longum* ssp. *Infantis*[9]. A study showed that preterm infants receiving mother's human milk had a more significant number of Bifidobacterium and Bacteroides, which protect the infants from morbidities like NEC[5,30]. Feeding VLBW infants with mother's breast milk was associated with an increase in gut microbial diversity and better growth compared to infants fed with human donor milk[30].

Short-chain fatty acids (SCFAs) such as acetate,

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propionate, and butyrate are dietary fiber fermentation products from probiotic bacteria. SCFAs modulate insulin sensitivity, systemic inflammation, as well as glucose and lipid homeostasis. SCFAs has a broad role in energy metabolism; it reportedly affects glucose metabolism through appetite regulation, intestinal gluconeogenesis induction, and gut-brain axis stimulation. SCFAs have also been reported to exhibit protective effects against inflammatory bowel disease, due to the fact that it supports enterocyte proliferation, increases barrier function through tight junction protein induction, and induces antimicrobial peptides and other anti-inflammatory effects[31].

SCFAs are abundantly produced when a microbe that can consume HMOs, such as *B. longum* ssp *infantis,* meets human milk. This process decreases fecal pH and suppresses facultative anaerobes such as Enterobacteria[27,31]. The production of SCFAs will be impaired If there is a disruption to the gut microbiota.

Unlike the constant composition in term milk, HMO composition in preterm milk fluctuates throughout lactation[32]. Therefore, some preterm newborn formula products have been added with non-human milk oligosaccharides such as lactulose, inulin, short-chain galactooligosaccharides (scGOSs), and long-chain fructooligosaccharides (lcFOSs) as substitutes for HMOs[14,25]. Different types of synthetic prebiotics offer different benefits. The combination of short-chain prebiotics and long-chain prebiotics mimics natural HMOs the best[25].

One meta-analysis of seven randomized controlled trials (RCTs) on prebiotic supplementation found that prebiotic oligosaccharides supplementation was well-tolerated and significantly increased the growth of Bifidobacteria but not resulted in decreased incidence of LONS, NEC, and time to full enteral feeds. The study also found that weight gain was not significantly affected[25]. The stimulation of Bifidobacteria was found to be associated with a reduced presence of clinically relevant gut pathogens[33].

Dasopoulou et al.[26] studied the impact of a prebiotics enriched formula with a combination of lcFOS and scGOS on preterm infants during the first 16 days of life. They had a more significant mean motilin increase and less gastric residue than those who received a typical preterm formula, although the gastrin level was not different between the two groups. However, the increase in low-density lipoprotein (LDL) and mean cholesterol was lower in the intervention group.

Niele *et al*.[34] found that the first year of life incidence of allergic and infectious diseases in preterm infants does not decrease with short-term supplementation of non-human neutral and acidic oligosaccharides via enteral route in the neonatal period. While other studies have stated that supplementation protects infants from atopic dermatitis, allergic rhinitis, allergic urticaria, and infections, it depends on the supplementation duration and dosage.

CONCLUSION

After birth, preterm infants face numerous challenges, including short and long-term morbidities, to survive and grow well with impaired immune and gastrointestinal systems. Beneficial gut microbiota has been known to influence both immune systems and intestinal motility and maturation while also reducing the pathogen overgrowth in the gastrointestinal tract. There is evidence that feeding preterm infants with breastmilk supplemented with prebiotics may support their gut microbiota and immune system.

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