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Perspektif Dokter Anak Indonesia Mengenai Peran Susu Formula dengan Suplemen Prebiotik bagi Imunitas, Pertumbuhan, dan Perkembangan Bayi Prematur: Data Pendahuluan

Perspective of Indonesian Pediatricians on the Role of Prebiotic-Supplemented Formula towards Immunity, Growth and Development in Preterm Infants: A Preliminary Data

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ABSTRAK

Latar belakang: *Belum matangnya imunitas bayi prematur berkaitan dengan disbiosis usus dan merupakan risiko kesehatan signifikan bagi pertumbuhan dan perkembangan bayi prematur. Pedoman penanganan bayi prematur saat ini hanya berfokus pada gizi makro dan mikro, sedangkan pencernaan bayi prematur perlu dioptimalkan untuk menunjang penyerapan zat gizi. Penelitian tentang dampak positif penggunaan prebiotik sebagai asupan pendamping telah dilakukan, namun belum diterapkan di Indonesia. Perspektif dokter anak Indonesia mengenai penemuan ini perlu diketahui.*
Tujuan: *Mendeskripsikan persepsi dokter anak Indonesia mengenai peran keseimbangan mikrobiota usus dalam menunjang imunitas, pertumbuhan, dan perkembangan bayi prematur, serta peran ASI dan susu formula dengan suplemen prebiotik dalam mengoptimalkan keseimbangan mikrobiota usus.*
Metode: *Dilakukan penelitian potong-lintang terhadap 114 Dokter Anak di Indonesia menggunakan kuesioner yang telah divalidasi dan digunakan dalam penelitian sebelumnya mengenai peran keseimbangan mikrobiota usus dan dampak disbiosis usus terhadap bayi prematur, serta peran ASI dan susu formula dengan suplemen prebiotik dalam mengoptimalkan keseimbangan mikrobiota usus.*
Hasil: *Sebagian besar responden setuju bahwa keseimbangan mikrobiota usus mendukung imunitas, pertumbuhan, dan perkembangan bayi prematur. Responden juga setuju bahwa ASI mengandung zat gizi yang mendukung keseimbangan mikrobiota usus, dan saat ASI tidak tersedia, susu formula dengan suplemen prebiotik dapat diberikan sebagai penggantinya.*
Kesimpulan: *Dokter anak Indonesia berpendapat bahwa keseimbangan mikrobiota usus berperan penting dalam imunitas, pertumbuhan, serta perkembangan bayi prematur, dan ASI merupakan nutrisi paling ideal bagi bayi prematur untuk mengoptimalkan keseimbangan mikrobiota usus. Susu formula dengan suplemen prebiotik dapat dipertimbangkan sebagai alternatif.*

Kata kunci: *Bayi Prematur, Imunitas, Pertumbuhan Dan Perkembangan, Susu Formula, Prebiotik*

ABSTRACT

Background: Immature immune system in preterm infants is associated with gut dysbiosis and poses significant health risks to their growth and development. Current guidelines for managing preterm infants focuses solely on macro- and micro-nutrients, whereas preterm infants' gastrointestinal system requires optimalization to support nutrient absorption. Studies on the positive impacts of prebiotics as supplements have been conducted, but has not been implemented in Indonesia. Indonesian pediatricians' perspective on these findings needs to be assessed.
Objectives: To describe the perspectives of Indonesian pediatricians on the role of gut microbiota balance in supporting immunity, growth, and development of preterm infants, and the role of breastmilk and prebiotic-supplemented formula in optimizing gut microbiota balance.
Methods: A cross-sectional study was conducted on 114 Indonesian pediatricians using a previously-validated and previously-used questionnaire on the role of gut microbiota balance on preterm infants, as well as the role of breastmilk and prebiotic-supplemented formula in optimizing gut microbiota balance.
Results: Most respondents agreed that gut microbiota balance supports immunity, growth, and development of preterm infants. Respondents also agreed that breastmilk contains nutrients that support gut microbiota balance and when breastmilk becomes unavailable, prebiotic-supplemented formula can be given as substitute.
Conclusions: Indonesian pediatricians considered gut microbiota balance to be important for immunity, growth, and development of preterm infants, and breastmilk to be the most ideal source of nutrition for preterm infants in optimizing

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gut microbiota balance. When breastmilk is unavailable, prebiotic-supplemented formula can be considered as an alternative.

Keywords: Preterm Infants, Immunity, Growth and Development, Formula, Prebiotics

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INTRODUCTION

Worldwide, preterm birth occurs in 11% births, ranging from 5% in several countries in Europe to 18% in some countries in Africa. It remains a significant cause of mortality and morbidity in children, accounting for approximately 35% of all newborn deaths. According to the World Health Organization's estimation, globally, 15 million preterm babies are born every year.[1,2] Although there have been advances in technology used to care for preterm infants, the burden of preterm births remain substantial as it poses health & developmental risks for the infants that may extend even into their adulthood,[3] and presents challenges for healthcare professionals.[4]

Preterm infants tend to have multiple immature systems, including immature immune system which makes them vulnerable to infections, such as necrotizing enterocolitis (NEC), early-onset neonatal sepsis (EONS), and late-onset neonatal sepsis (LONS).[2,5] Preterm infants are also prone to gut dysbiosis, as the gut microbiota establishment is prone to alterations and imbalance due to immature organs, use of antibiotics, and medical interventions.[6] Gut dysbiosis, in turn, affects immune system development in preterm infants, as gut microbiota is known to modulate the immune system.[7] In previous studies, altered gut bacterial composition has been linked to the pathogenesis of infection and inflammatory disorders in preterm infants, resulting in long-term neurological outcomes such as necrotizing enterocolitis and sepsis, and impairing their growth and development.[8]

Early colonization of gut microbiota also plays an important role the development of both the innate and the adaptive immune systems. This was thought to have been associated with Th1 and Th2, which are needed to maintain immunologic balance and promote tolerance.[9] As such, disruption to this colonization process impacts preterm infants' immune system. Although studies reporting the exact prevalence of the clinical outcomes of gut dysbiosis remains limited, several studies have demonstrated links between gut dysbiosis and allergic diseases. Pascal, *et al*. reported that gut dysbiosis also disrupts mucosal immunological tolerance, which may result in allergic diseases such as food allergy and asthma. Low IgA levels at the intestinal surface barrier can also contribute to food allergy.[10] A study by Chiu, *et al*. also demonstrated that there is a link between dysbiosis of particular subsets of the gut microbiota and IgE-mediated allergic responses for allergic rhinitis and asthma in early childhood.[11] This highlights the need for a reliable treatment for gut dysbiosis in preterm infants.

Breastmilk is often used to boost postnatal growth and organ development by stimulating the maturation of not only the gastrointestinal tract, but also the gut microbiota and immune system as well.[12] Breastmilk contains immunomodulatory components, such as sIgA and lactoferrin, that modulate intestinal microbiota known to play a role in inhibiting the development of allergies. It is also rich in immune cells that can compensate immature immune system in preterm infants, and in tolerogenic cytokines such as IL-10 and TGF-β that increases infants' immune tolerance against various antigens.[13,14] The two major component of breastmilk is the human milk oligosaccharides (HMOs) and milk microbiota that influence the infant gut microbiota and the development of their immune system. HMOs exert a selective pressure within the infant gut microbial niche, promoting the proliferation of specific bacteria including *Bifidobacteria*. Breastmilk is also a source of viable bacteria originating from the maternal gut and infant oral cavity. Therefore, breastmilk has prebiotic and probiotic properties.[15] Breastfeeding has been proven to have protective effects against allergic disease, including asthma, when given exclusively for 6 months. It has also been proven to be protective against childhood asthma when administered exclusively for 4 months.[14,15]

While breastmilk can act as natural treatment for gut dysbiosis, breastfeeding preterm infants presents another set of challenges, as preterm infants tend to have poor sucking-swallowing reflex, making effective breastfeeding almost impossible for them for days, weeks, or sometimes months after birth.[16,17] In Indonesia, despite campaigns from the Ministry of Health to promote exclusive breastfeeding, several barriers to exclusive breastfeeding has also been identified, including parents' misconception about breastfeeding, influence and pressure from family and community members, the mothers' psychological condition, healthcare workers' lack of awareness and knowledge, as well as the mother's low quantity of breastmilk. Lack of systematic support to breastfeeding has also been cited as barriers to exclusive breastfeeding in Indonesia.[18] In Indonesian hospitals, several factors were thought to contribute to the low rates of early exclusive breast-feeding, including the quality and quantity of breast-feeding education; misunderstandings that arises from infant formula manufacturers marketing materials; limited hospital infrastructure; inconsistent policy, legislation and protocols; and perceived need for infant formula supplementation.[19] In conditions where breastfeeding is impossible, it is necessary to provide

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additional nutrients to act as supplements for the infants, especially preterm infants, in order to support their growth and development.[17]

Prebiotics have important potentials in supporting the clinical outcomes related to gastrointestinal health and immunity in preterm infants. The term prebiotic refers to substrates utilized selectively by its host microorganisms to confer health benefits. Prebiotics may also have immunoactive properties, and may be beneficial in improving health and preventing juvenile diseases.[20] Prebiotic supplementation in preterm infant formula is thought to have positive impact on the gut microbiota as a substitute for human milk oligosaccharides (HMO), the third most prevalent and most essential component in breastmilk.[21] These substances protect against infection and may be able to alleviate the course of infection through various mechanism, as they have been shown to exhibit anti-bacterial, anti-viral, and anti-inflammatory properties.[22] Supplements containing galacto- and fructo-oligosaccharides (GOS and FOS), more specifically, are manufactured to function similarly to HMOs and have been shown to have positive benefits for immune system development.[23] Vandeplas, *et al*. in their study reported evidence that adding oligosaccharides prebiotics to infant formula helps bring the GI microbiota of formula-fed infants close to the microbiota composition of breastfed infants.[24] A study by Bertelsen, *et al*. reported that probiotics and prebiotics supplementation in infant formula may provide benefits in reducing the risk of NEC in preterm infants and may help in the treatment of acute gastroenteritis in older children, although its long-term risks remain unclear.[25] A study by Kona and Matlock further detailed the benefits for prebiotics supplementation in preterm infants formula. They reported that the administration of prebiotics supplements in infant formula are associated with several physiological changes such as decreased gastrointestinal transit time, stool viscosity, and pH, although these changes were not associated with clinical improvement of NEC, LONS, and time to full enteral feeding.[26] Bering's study similarly found that limited evidence on the clinical benefits of prebiotics supplemented formula in the preterm neonates' first weeks of life. However, Bering also found that introducing HMOs when the preterm neonates have developed sufficient adaptation to bacterial colonization and feeding have beneficial effects in their gut health.[27]

Despite these growing evidences for the role of gut microbiota in improving immune system and supporting the growth and development of preterm infants, as well as evidences of prebiotic supplementation in modulating gut microbiota in preterm infants, available current guidelines – both national and international – remain focusing more on the provision of macro- and micro-nutrients in order to catch-up growth in preterm infants.[14,28] The Indonesian Pediatric Society currently does not recommend the provision of prebiotics, probiotics, and synbiotics in the prevention of allergies.[14] While the World Allergy Organization does not support the use of prebiotics supplementation in exclusively breastfed infants, it does support its provision to non-exclusively breastfed infants, whether or not they are at high or low risk for developing allergy.[29] The fact that there were limited recommendations on the use of prebiotic supplementation to improve the immunity, growth, and development of preterm infants, despite increasing evidences of its benefits towards immunity, raises the question on what are the perspectives of pediatricians on the role of immunity and gut microbiota balance in supporting preterm infants' growth and development. We conducted a survey especially on Indonesian pediatricians to gather information on their perspectives on the role of immunity and gut microbiota balance in supporting preterm infant growth and development, as well as the role of prebiotic-supplemented formula as a breastmilk substitute in the immune system development of preterm infants, should breastmilk for some reasons become unavailable. This will serve as preliminary data for future research and innovations in terms of the use of prebiotics in in the treatment of preterm infants in Indonesia.

METHODS

This is a cross-sectional study conducted from January to February 2021. One-hundred-and-fourteen Indonesian pediatricians were asked to complete an online survey using the Google-form survey platform. Respondents were recruited using convenience sampling method and sample size was determined using a sample size calculation table proposed by Singh and Masuku, which stated that for a population size of 5000-7000, a 98-99 samples is sufficient to provide reliable data.[30] According to 2020 data published by the Ministry of Health of Indonesia, there are a total of 6084 pediatricians in Indonesia, indicating that a minimum of 99 respondents would be sufficient to provide a reliable data. All respondents were recruited at scientific events and visited by Danone Medical Representatives, whose identity was obscured to ensure subjects' independence from brand image. The representatives then asked the participants to complete a 15-question questionnaire that had previously been validated and used in other studies.[31–33] All participants have consented to complete the questionnaire. No ethical clearance was obtained due to the non-experimental nature of this study.

The 15-question questionnaire involved 6 demographic questions and 9 multiple-choice questions about immunity in preterm infants, gut dysbiosis and the health risks it poses to preterm infants, as well as the benefits of breastmilk in immunomodulation. The participants' perspective on the benefits of prebiotics-supplemented preterm formula in providing essential nutrients for immune system development in the absence of breastmilk was also assessed. The resulting data is presented in the following descriptive report.

RESULTS AND DISCUSSION

A total of 114 respondents participated in this survey, all of which were pediatricians, including 11 neonatologist consultants. Respondents came from various cities in Sumatra, Java, Bali, Kalimantan, Sulawesi, and Nusa Tenggara. More than 70% of

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respondents have more than 5-years' experience and the majority of respondents (67%) worked in government hospitals in various cities in Indonesia. Most of the respondents (45%) had 5-10 preterm infants consulted to them in the month prior to the study, while 23% of respondents had more than 10 infants consulted to them. **Table 1** shows the demographic characteristics of the respondents. In terms of risks faced by preterm infants, the respondents presented quite a similar view, as 93.9% of respondents chose immature GI tract (including risk of gut dysbiosis) as the most significant risk faced by preterm infants. Other significant answers include risk of infection (88.6%), faltering growth and development (88.6%) and poor neurodevelopmental outcomes (88%). Details are presented in **Figure 1**.

Table 1. Respondents' demographic characteristics

	Description	n	%
Age	30-39	31	27.19
	40-49	57	50.00
	≥50	26	22.81
Specialty	Pediatrician	103	90.35
	Neonatologist (Consultant)	11	9.65
Experience	≤5 years	26	22.81
	6-10 years	37	32.46
	11-15 years	33	28.95
	>15 years	18	15.79
Institution	Private	47	41.23
	Government	67	58.77

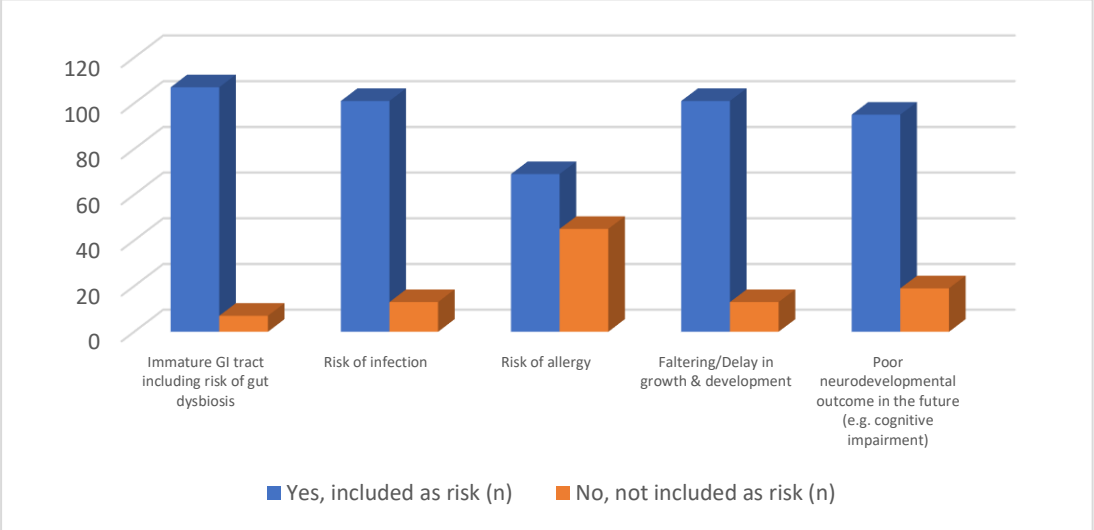

Figure 1. Healthcare Professionals' Perspective on the Risks Faced by Preterm Infants

Preterm infants, as defined by the World Health Organization (WHO), refers to infants born before 37 completed weeks of gestation, or infants born less than 259 days since the first day of the mother's last menstrual period (LMP).[34] Despite advancements in technology and neonatal care, this population remains are at increased health risks, including death and other medical complications,[35] mostly due to their immature organ systems.[2] In addition to immediate health risks due to preterm birth, preterm infant may also face long-term consequences due to developmental impairment and chronic health problems.[36]

To determine the proper management strategy to care for preterm infants, it is essential to first understand the perspectives and attitudes of healthcare professionals towards the health risks of infants born prematurely. Studies have shown that healthcare professionals' attitude and belief are significantly associated with the clinical management of a disease.[37,38] Evidences have also shown that healthcare professionals' perspectives and attitudes may affect the decision-making process involved in the management of preterm infants in NICU settings.[38–40]

Our study found that more than 88% respondents chose GI tract immaturity (including risk of gut dysbiosis), risk of infection, faltering growth & development and poor neurodevelopmental outcome as significant risks for preterm infants. Preterm infants are particularly at risk of gut dysbiosis, especially due to their immature gastrointestinal systems.[4] Exposure to conditions which can modify the process of acquiring normal microbiota also renders preterm infants vulnerable to dysbiosis, which can influence their health and well-being.[4] Exposure to conditions which can modify the process of acquiring normal microbiota also renders preterm infants vulnerable to dysbiosis, which can influence their health and well-being.[7] The GI tract begins as a simple tubular structure that forms in the

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fourth week of gestation. It quickly polarizes along its anterior-posterior axis. The embryological gastrointestinal structure consists of 3 sections: the foregut, midgut, and hindgut; out of which all gastrointestinal organs would later develop.[41] While the anatomical development of all gastrointestinal organs are typically completed by the 21st week of gestation, the development of its digestion, absorption and motility functions continue well beyond that, extending even after birth.[42] As these crucial functions of the gastrointestinal system were still on development at their birth, infants born prematurely have particular challenges related to abnormal motility and inefficient absorption and digestion of nutrients, which may manifest as reflux and feeding intolerance.[41]

Fetal immune system development begins at 4-6 weeks of gestation and remains in development even after term birth.[2,43] As such, immature immune system tend to be more pronounced in preterm infant,[2] as can be seen in their disproportionate white blood cells count and impaired innate response towards pathogens.[44] Additionally, newborns also rely on passively-acquired antibodies from their mothers to protect against infections due to their developing adaptive immune response.[43] Maternal antigen-specific immunoglobulin (IgG) is transferred through the placenta in large amounts after 32 weeks of gestation, and continues throughout the third semester, as the fetal immune system prepares for postnatal immune defense. Disruption to this process due to premature birth leads to low maternal IgG levels and deficiencies and phagocytotic activities, increasing the risk of infection in preterm infants.[2,45]

The most critical phase of brain development occurs at the late second and third trimester of pregnancy, where increasing cortical surface area, formation of interneuronal connection, myelination, the growth of dendrites and axon, as well as synaptogenesis took place. Synaptic pruning and myelination are even more prominent during late gestation and infancy. This process is often disrupted in preterm infants, resulting in changes in the brain volume and microstructure associated with neurodevelopmental impairment.[46,47] Disrupted brain development in preterm birth tend to have several long-term repercussions in the form of multidomain brain dysfunction, including general intelligence, attention, executive function, memory, language, and motor skills.[48] Preterm infant may also experience fine or gross motor delay, cerebral palsy, impaired vision and/or hearing loss and other forms of sensory impairment, impaired cognitive skills that cause difficulties in learning and communicating, as well as behavioral and psychological problems.[49,50]

Figure 2 shows that most respondents (>98%) agreed that the immune system could support, at least partially, the growth of preterm infants. They also agree that the balance of gut microbiota plays supports immune development in preterm infants, and that the risk of gut dysbiosis significantly impacts the immune system as well as the growth and development in preterm infants, both in the short- and long-term.

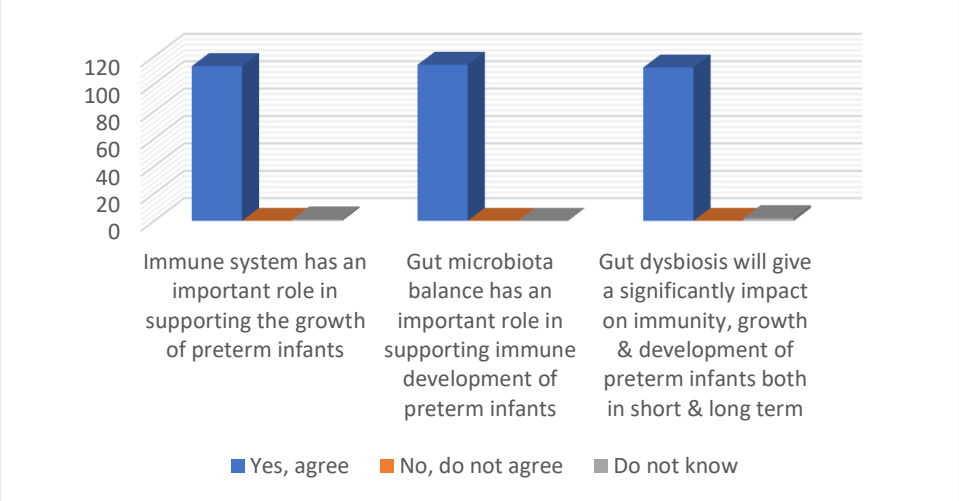

Figure 2. Healthcare Professionals' Perspective on the Role of the Immune System and Gut Microbiota in the Growth and Development Preterm Infants

Gut microbiota allegedly plays a role in various diseases such as allergy, autoimmune disease, infections, colorectal cancer, and metabolic diseases; where disruption of microbiota composition, known as dysbiosis, is often cited as the aggravating factors for these diseases.[51] Many factors, including mode of delivery (vaginal vs caesarean), antibiotic exposure, and formula feeding, influence the development of gut microbiota in preterm infants. All of these factors influence gut colonization and may play a role in the pathogenesis of necrotizing enterocolitis and feeding intolerance.[52] Moreover, intrauterine infections or dysbiosis might also results in preterm birth[52,53] and other maternal factors, such as obesity, diet, smoking, and antibiotic use, also factors into the infant's gut microbiota, predisposing them to metabolic syndromes, atopic dermatitis, and allergy in their childhood.[54]

Given that the gut microbiota also plays an important role in the immune system development of preterm infants, disruption or dysbiosis of this

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microbiota may have an impact on their developing immune systems.[55] The gut microbiota, which houses beneficial commensal bacteria essential to support digestion, maintain homeostasis, regulate intestinal immune function, and protect from injury, helps protects against pathogens and toxins.[7] Previous studies have linked the disruption of gut microbiota in preterm infants to the pathogenesis and development of infectious diseases such as necrotizing enterocolitis (NEC), and early- and late-onset neonatal sepsis.[2,5,7]

Data from animal and human studies has increasingly suggested that the gut microbiome has enormous impact on behavioral and stress responses later in life, particularly at early postnatal stages. Gut-brain axis implies that the complex functions of the brain rely also not only on the sympathetic-parasympathetic and the enteric nervous system but on endocrine homeostasis as well, and they impact on each other bidirectionally.[56,57] Preterm infant gut dysbiosis has been linked to a number of neurodevelopmental disorders that can affect the child's life well into adulthood, including autism spectrum disorders, attention deficit hyperactivity disorder, and schizophrenia spectrum disorder.[58]

The majority of our respondents (98%) agreed that breastmilk contains immunomodulator & nutrients including oligosaccharide that support the immune development of preterm infants, and 93% of respondents agreed that prebiotics will support the immune development of preterm infants through gut microbiota modulation. This is presented in **Figure 3**.

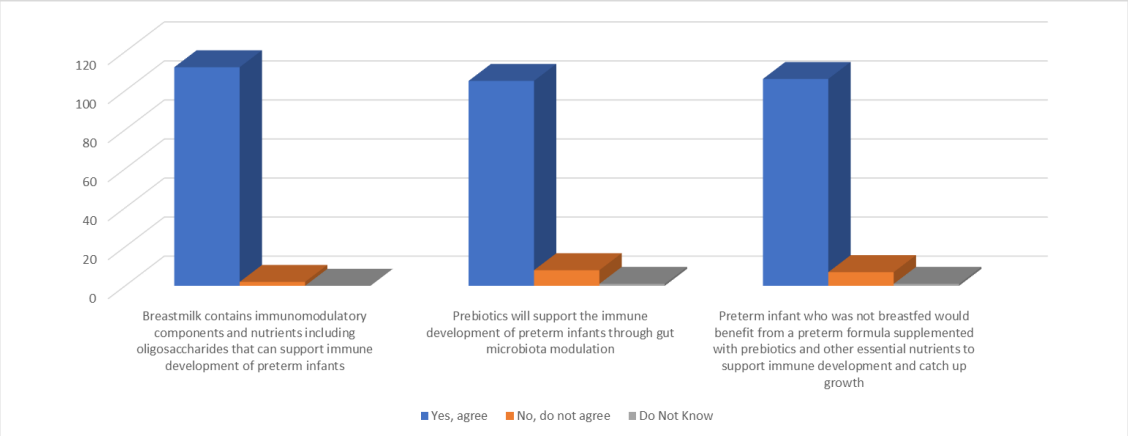

Figure 3. Healthcare Professionals' Perspective on the Role of Breastmilk and Prebiotic-Supplemented Preterm Formulas in the Growth, Development, and Immunomodulation of Preterm Infants

Nutrition is essential for preterm infants' growth and development, metabolism, and immunity establishment, and studies have shown that poor nutrition is associated with poorer brain growth, resulting in poor psychomotor development and mental skills.[59,60] Breastmilk is considered to be the best food for infants, and has been known to stimulate maturation of the gastrointestinal tract, as well as gut microbiota and immune system, which promotes postnatal growth and organ development.[12] A robust microbiota have been demonstrated to result from breastfeeding, reducing the infant's susceptibility to NEC and LOS, and indicating that breastmilk plays an significant role in the development of a healthy immune system.[61] Additionally, infants fed their mother's breastmilk had a more diverse gut microbiota and grew faster than infants fed human donor milk, according to studies.[62] However, feeding preterm infants with breastmilk presented another challenge, due to their immature neurodevelopment often resulting in poor sucking-swallowing reflex. Other medical conditions may also render the mother to be unable of breastfeeding. Moreover, in preterm breastmilk, the amount of protein and essential minerals such as sodium, phosphate, and calcium may not be sufficient to meet the infant's nutritional needs.[16] When breastfeeding is impossible, it may be necessary to supplement the infant's nutrition with a preterm formula.[16,17]

As much as 93% of respondents agreed that in the absence of breastmilk, preterm formula supplemented with prebiotic and other nutrients will support immune development and catch-up growth of preterm infants. Prebiotics refer to non-digestible dietary supplements that provide a substrate of nutrient to stimulate the growth of health-promoting gut microbiota.[63] Prebiotics may also have immunoactive properties, and may be beneficial in improving health and preventing diseases often experienced by pediatric patients.[20] Providing prebiotics to preterm infants has been linked to the proliferation and promotion of probiotic bacteria growth in the intestinal tract, prevention of pathogens overgrowth, and promotion intestinal mucosa maturation.[64]

Human milk oligosaccharides (HMOs) contained in breast milk are the most accessible source of prebiotics, and as such it has been used as prebiotic supplements in many infant formulas. These natural oligosaccharides have been shown to prevent diseases such as retinopathy of prematurity, and cognitive impairment, NEC, nosocomial infection, late-onset sepsis,[12] in addition to protecting preterm infants from immune-related conditions, including allergies,

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autoimmune diseases, and chronic noncommunicable diseases in later life stages.[65] These substances could provide protection against infection and may be able to alleviate the course of infection through various mechanism, as they have also been shown to exhibit anti-bacterial, anti-viral, and anti-inflammatory properties.[22]

Several studies have shown that prebiotic oligosaccharides supplementation provided beneficial effects to preterm infants' gastrointestinal functions. It is well-tolerated and significantly increased the growth of probiotic bacteria growth in the intestinal tract. However, these formulas could not completely emulate the microbiota of breastfed infants; thus, non-human milk oligosaccharides such as short-chain galactooligosaccharides (scGOSs), long-chain fructooligosaccharides (lcFOSs), inulin, and lactulose have been added to preterm infant formula products to function similarly to HMOs as prebiotics. This suggests that the microbiome and immune responses play a role in neurodevelopmental processes.[66] A study by Vandeplas, *et al.* in 2015 reported evidence that adding oligosaccharides prebiotics to infant formula helps bring the GI microbiota of formula-fed infants close to the microbiota composition of breastfed infants.[24] Another study by Bertelsen, *et al*. also reported that supplementation of prebiotics in infant formula may reduce the risk of NEC in preterm infants and may help in the treatment of acute gastroenteritis in older children, although its long-term risks remain unclear.[25] A study by Kona and Matlock further reported that the administration of prebiotics supplements are associated with several physiological changes such as decreased gastrointestinal transit time, stool viscosity, and pH. These changes, however, were not associated with clinical improvement of NEC, LONS, and time to full enteral feeding.[26] A study by Bering found similar result of limited evidence on the clinical benefits of prebiotics supplemented formula in the preterm neonates' first weeks of life. However, Bering noted that later introduction of HMOs when the preterm neonates have sufficiently adapted to bacterial colonization and feeding have beneficial effects in their gut health.[27]

CONCLUSION

Our study demonstrated that the majority of healthcare professionals recognizes preterm birth as posing significant health risks to infants born prematurely, including risks of immature gastrointestinal system leading to gut dysbiosis, risks of infection, and risks of faltering growth and development; and as such, gut microbiota balance plays an important role in supporting preterm infants' immunity, growth, and development. Moreover, healthcare professionals agree that breastmilk is the ideal nutrition for preterm infants as it contains immunomodulator and nutrients essential for their growth and development. In the absence of breastmilk due to medical conditions, preterm formula supplemented with prebiotics may be considered as alternative to support the immune development as well as the preterm infants' growth and development.

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