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Tata Laksana dan Rekomendasi Gizi Bagi Bayi Prematur: Sebuah Kajian Pustaka

Nutritional Management and Recommendation for Preterm Infants: A Narrative Review

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ABSTRAK

Latar Belakang: *Kelahiran prematur, yang didefinisikan sebagai kelahiran pada usia 37 minggu kehamilan, merupakan prediktor paling penting dalam kesehatan dan perkembangan bayi. Kelahiran prematur merupakan penyebab utama kematian pada anak di bawah 5 tahun di seluruh dunia dan menyebabkan sekitar 1 juta kematian neonatus. Kelahiran prematur berperan besar dalam meningkatkan angka morbiditas pada anak-anak dengan risiko disabilitas yang tinggi dan kualitas hidup yang buruk.*
Tujuan: *Tujuan artikel ini adalah untuk menjabarkan kondisi bayi prematur, apa yang membedakannya dari bayi yang lahir aterm, dan apa yang perlu dipertimbangkan dalam tata laksana gizi bayi premature melalui suatu tinjauan pustaka naratif tradisional.*
Ulasan: *Bayi premature memiliki risiko untuk mengalami komplikasi yang lebih besar dibandingkan bayi aterm dengan laju mortalitas dan morbiditas yang lebih tinggi. Morbiditas dan mortalitas bayi prematur dapat diturunkan melalui intervensi tepat waktu yang diberikan baik bagi ibu maupun bagi bayinya. Intervensi maternal, seperti edukasi kesehatan dan pemberian suplementasi gizi mikro, diberikan sebelum atau selama kehamilan dan saat persalinan, sementara perawatan bagi bayi prematur harus dimulai segera setelah lahir, mencakup pemberian air susu ibu (ASI) lebih dini dan optimalisasi penambahan berat badan.*
Kesimpulan: *Perawatan esensial dan tata laksana gizi yang agresif bagi bayi prematur dapat mendukung perkembangan yang cepat dan meningkatkan luaran neurodevelopmental. Tujuan terapi bagi bayi prematur bukan hanya agar bayi tersebut dapat bertahan hidup melainkan juga agar bayi tersebut dapat bertumbuh dan berkembang tanpa morbiditas residual.*

Kata Kunci: *Prematur, Bayi, Pertumbuhan, Perkembangan, Gizi*

ABSTRACT

Background: Preterm birth is defined as birth before 37 completed weeks of pregnancy. It is the most important predictor of adverse health and development infant outcomes that extend into the early childhood and beyond. It is also the leading cause of childhood mortality under 5 years of age worldwide and responsible for approximately one million neonatal deaths. It is also a significant contributor to childhood morbidities, with many survivors are facing an increased risk of lifelong disability and poor quality of life.
Purpose: In this article, we aimed to describe features of preterm infants, what makes them different from term infants, and what to consider in nutritional management of preterm infants through a traditional narrative literature review.
Discussion: Preterm infants are predisposed to more health complications than term infants with higher morbidity and mortality. This morbidity and mortality can be reduced through timely interventions for the mother and the preterm infant. Maternal interventions, such as health education and administration of micronutrient supplementation, are given before or during pregnancy and at delivery, whereas appropriate care for the preterm infants should be initiated immediately after birth, which include early breastfeeding and optimalization of weight gain.
Conclusion: Essential care of the preterm infants and early aggressive nutrition should be provided to support rapid growth that is associated with improved neurodevelopmental outcomes. The goal is not only about survival but making sure that these preterm infants grow and develop without any residual morbidity.

Keywords: *Preterm, Infants, Growth, Development, Nutrition*

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INTRODUCTION

The World Health Organization (WHO) estimated that each year, 15 million babies are born preterm globally. It occurs in more than 1 in 10 babies worldwide, and the global trend is still rising. Across 184 countries, the global preterm birth rate is approximately 11%, ranging from 5% in some countries in Europe to 18% in some countries in Africa.[1,2] In Indonesia the estimated preterm birth rate is 10.4% which contributed 3.5% of global preterm birth rate.[3] It has been known that preterm birth, which is defined as birth before 37 weeks of pregnancy, is the most important predictor of adverse health and development infant outcomes that extend into the early childhood and beyond.[4] It is the most frequent cause of mortality in children under 5 years worldwide and responsible for approximately one million neonatal deaths in 2015.[1,2,5]

Preterm birth is also a significant contributor to childhood morbidities, with many survivors are facing an increased risk of lifelong disability and poor quality of life.[6,7] These include neonatal morbidities, delays in motor, cognitive, and behavioral development during early years of childhood, learning disabilities, visual and hearing problems, as well as increased risk for chronic diseases such as cardiovascular disease and diabetes later in life.[8]

A variety of risk factors have been associated with preterm birth, such as maternal age (too young or too old), parity (>4), multiple pregnancy, maternal urinary tract infections, prior preterm birth, hypertension during pregnancy, prolonged premature rupture of membranes, antepartum hemorrhage, substance use (tobacco, alcohol, drugs), and maternal or fetal stress.[9,10] In Indonesia, the substantial risk factors for preterm birth are poor antenatal care, repeated preterm birth, young mother, maternal diseases (hypertension and anemia), premature rupture of membranes, antepartum bleeding, and vaginal discharge.[11] Good nutritional status of the mother will improve the outcome of both mother and newborn.[11] Preterm neonates are given human milk or formula orally and enterally depending on the conditions.[12] Probiotics are added as soon the neonate is stable to improve the feeding intolerance.[13]

In this article, we aim to describe, through a traditional narrative literature review, the features of preterm infants, what makes them different from term infants, and what to be considered in managing preterm infants, particularly nutritional management, which are essential in improving preterm infants' long-term outcomes.

DISCUSSION

DEFINITION OF PRETERM INFANTS

According to the World Health Organization (WHO), babies born alive before 37 completed weeks of pregnancy, or less than 259 days since the first day of the mother's last menstrual period (LMP), are considered preterm infants. Based on gestational age (GA), preterm infants are further classified as extremely preterm (<28 weeks gestational age), very preterm (28 to <32 weeks gestational age), moderate preterm (32 to <34 weeks gestational age) and late preterm (34 to <37 weeks gestational age).[7,14]

Preterm infants also tend to be smaller compared to term infants. Being preterm and small for gestational age are the reasons for low-birth-weight (LBW), which also pose an indirect impact on neonatal mortality and morbidity.[15–17] The WHO defines low-birth-weight as a birth weight of less than 2500 g. They further categorized low-birth weight babies into very low-birth-weight (weighing less than 1500 g at birth) and extremely low-birth-weight (weighing less than 1000 g at birth).[18]

FACTORS AFFECTING THE OUTCOMES OF PRETERM INFANTS

Recent studies have indicated that poor growth of preterm infants during the first 1000 days are related to a disrupted gut-brain axis,[19] alterations in gut microbiota composition,[20–22] less-than-adequate nutrition,[23] and the presence of prematurity complications.[24] The gut microbiota, which assemble and stabilize during the first 1000 days of life, is known to affect growth via regulation of growth hormone and IGF-1 production. Immature or delayed assembly of the gut microbiota may also cause inflammation and enteropathy.[22] Altogether, the dysbiosis of gut microbiota may increase the risk of feeding intolerance,[25] NEC, malnutrition and eventually lead to growth faltering in preterm infants.[26]

Aside from physical growth, emerging evidence shows that the colonization of gut microbiota in the early life plays an important role in the formation and maturation of the immune system[27] as well as developmental pathways;[28] and that disruption of this process is associated with lifelong neurodevelopmental deficit as well as increased risk of developing chronic diseases.[22]

A number of factors have been found to influence the colonization of gut microbiota after birth. The primary factors include mode of delivery (vaginal vs caesarean), gestational age, early use of antibiotics, and feeding methods (human milk vs formula).[19,29]

Based on these facts, a window of opportunity exists in the first 2 years of life to modulate the gut microbiota through proper nutritional management in preterm infants, which in turn promotes healthy growth and development.

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DIFFERENCES OF PRETERM INFANTS & TERM INFANTS

Physical appearance at birth

Preterm infants are small in size, with a disproportionately large head.[30] They tend to look skinny, due to lack of body fat and have thin, hairy, pink skin through which the underlying veins are easily seen.[31] Muscle tone is notably different in preterm and term infants. At the first assessment, preterm infants had lower scores in all muscle tone indicators.[32] This is the reason why extremities are not held in the flexed position typical of term infants. Preterm infants also show minimal resistance to passive manipulation in all extremities.[31]

The reflexes shown depend on gestational age. Extremely preterm infants won't have any reflex until they reach 28 weeks gestation where Moro reflex and palmar reflex begin to develop. Meanwhile, the tonic neck reflex and stepping reflex will start to develop at 35 weeks. The former will be most prominent at 1 month after birth.[33] Preterm infants are also lacking in reflexes for sucking and swallowing that could lead to feeding difficulties.[34] Periodic breathing can be seen in preterm and term infants. However, it occurs more often in preterm infants.[35]

Growth and development

Most preterm infants will experience catch-up growth within the first 3 years of life.[36,37] To date, there is no consensus regarding monitoring of the preterm infants' growth or ideal growth rate. Fenton charts and INTERGROWTH-21st Preterm Postnatal Growth Standards can be used to monitor the growth of preterm infants although both charts have limitations.[38] As preterm infants, especially with extremely preterm birth, often suffers from extrauterine growth restriction, optimalization of nutrition care should be sought. Protein and energy intake on the first week of life, early aggressive nutrition, and additional supplementation are associated with good outcomes in preterm infants in relation to growth, development, and overall health status.[39]

However, neurodevelopmental outcomes may not always comparable to full-term infants. A longitudinal cohort study in Australia found that moderate and late preterm children exhibited delay development in cognitive, language, and motor skills. They also showed poorer social competence at 24 months' corrected age.[40] Another study showed that developmental problems in preterm infants may not emerge until preschool or kindergarten years, particularly in the language domain.[41]

COMMON CHALLENGES AND RISKS

Being born too early possesses some risks and challenges. In general, preterm infants have an increased risk of neonatal mortality and morbidity than term infants. The rate of mortality, incidence, as well as the severity of health complications increase as the gestational age and birth weight decrease.[42] Health complications in the preterm infants are categorized into short-term and long-term complications. Short-term complications result from functional and anatomic immaturity in the neonatal period and increases the risk of having long-term sequelae. Meanwhile, long-term complications occur in survivors after being treated in the neonatal intensive care unit (NICU). Similar to other low-middle income country, Indonesia experiences risks and challenges when treating preterm infants more than those in high income countries. Preterm is associated with significant morbidity and mortality. Severe infections e.g., sepsis, pneumonia, and necrotizing enterocolitis are commonly identified in these preterm infants. Furthermore, difficult access to healthcare facilities, short-staffed, and limited resources contributed to poor outcomes of preterm infants in Indonesia.[43]

SHORT-TERM COMPLICATIONS

Hypothermia

Preterm infants are vulnerable to rapid heat loss, owing to their relatively large body surface area, lack of body fat, as well as the inability to produce enough heat by shivering.[44] The risk of hypothermia is highest immediately after birth.[45] Hypothermia in preterm infants has been reported to be associated with breathing problems (respiratory distress syndrome), intraventricular hemorrhage (IVH), hypoglycemia, acidosis,[45,46] as well as increased neonatal mortality and morbidity.[47,48] In Indonesia, hypothermia is still a problem for preterm infants despite being more humid and tropical country. Cold stress and poor development of preterm infants' skin are several factors contributing to the incidence of hypothermia. Incubator or radiant warmer is often utilized to manage these problems.[49] Nutritional management in the form of early breastfeeding can also help managing hypothermia.[50]

Respiratory abnormalities

Prematurity in preterm infants may cause the following respiratory problems: (1) respiratory distress syndrome (RDS), previously called hyaline membrane disease, is caused by surfactant deficiency in an immature lung. The incidence of RDS is inversely related to gestational age. It is more severe in smaller and more preterm neonates. Despite improvement in management of infants with RDS, it remains the leading cause of morbidity and mortality in preterm infants;[51] (2) Bronchopulmonary dysplasia (BPD), or neonatal chronic lung disease, is a late respiratory complication commonly occurs in infants born at $\leq$32 weeks gestation or very low-birth-weight (VLBW) infants. Infants with this condition require oxygen supplementation at 36 weeks postmenstrual age (PMA).[52] An important long-term complication associated with BPD is pulmonary artery hypertension;[53] and (3) Apnea of prematurity, which occurs as a direct consequence of lung immaturity, constitutes as a cessation of breathing for 20 seconds or more, or a shorter episode accompanied by hypoxemia (cyanosis, pallor) and/or bradycardia (<100 beats per minute). The incidence, frequency and severity of symptoms increases with decreasing GA.[54]

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Respiratory problems are one of the most common obstacles found when treating preterm infants. In Indonesia, respiratory distress is more common than BPD or apnea of prematurity. Adequate intake during therapy is crucial to improve the outcomes. Both human milk, formula, and combination of human milk and Human Milk Fortifier (HMF) can be administered to improve the nutritional status. Wijaya et al. reported administration of human milk as enteral nutrition for neonates with respiratory problems. The weight gain target is 15-20 grams/kg/day. If the neonates have weight under 50th percentile, combination of human milk and HMF is used.[55]

Cardiovascular abnormalities

The main cardiovascular complications often observed in preterm infants include: (1) Patent ductus arteriosus (PDA). This abnormality commonly occurs in preterm infants, especially those who suffer from respiratory distress syndrome. The incidence of PDA is about 38% of in very low-birth-weight (VLBW) infants;[56] and (2) Systemic hypotension. Low blood pressure, without evidence of shock, is commonly observed in extremely low-birth-weight (ELBW) infants. Left untreated, this condition may result in significant mortality and morbidity (e.g., intraventricular hemorrhage) in preterm infants.[57]

In Indonesia, PDA is the most common congenital heart diseases identified in preterm infants. Aside from preterm labor, PDA is also associated with low birth weight which correlates with nutritional status.[58] Hence, optimizing nutrition is important for improving the outcome. Similarly with nutritional management for respiratory problems, human milk, formula, and combination of human milk and HMF can be considered with additional vitamin and mineral supplementation.[59]

Intraventricular hemorrhage

The incidence and severity of IVH increases as the birth weight and GA decrease. The most severe IVH occurs in VLBW and/or very preterm infants. Aside from prematurity, other factors that affect the risk of IVH include mechanical ventilation, pulmonary hemorrhage, respiratory distress, chorioamnionitis, pneumothorax, sepsis, asphyxia, and patent ductus arteriosus.[60] Hemodynamic instability and conditions that impair cerebral autoregulation also contribute to the occurrence of IVH. A study in a tertiary referral hospital in Indonesia reported that 43.47% of the preterm infants suffered from IVH with 7.6% of them having severe IVH. Prematurity and low birthweight were associated with IVH.[61] Although the main treatment for IVH is surgery and medications, optimalization of nutritional intake is important to avoid complications and improving the outcomes, especially after invasive methods.[62]

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is the most frequently-observed life-threatening emergency condition in the neonates, especially very low-birth-weight and preterm infants born before 32 weeks gestation. It occurs in 1-3 per 1,000 live births. It is associated with a high mortality rate of between 15 and 30%.[63,64] Survivors of NEC have an increased risk for delay in growth and neurodevelopmental abilities, as well as long-term sequelae such as persistent loose stools or frequent bowel movement.[65,66]

To date, its pathogenesis remains unclear and no particular causal pathogen has been identified. Many factors play a role in the occurrence of NEC, but recently, there is growing understanding of the relationship between compositional alterations referred to as gut dysbiosis, overall neonatal gut microbiota, and NEC.[67,68] Studies have shown that the gut microbiota of preterm infants has less diverse bacterial species and colonies, as well as higher proportions of potential pathogens when compared to term infants,.[26,69] Various factors are implicated in the pathogenesis of gut dysbiosis in preterm infants, such as maternal use of antibiotics, different constituents of human milk in mother with preterm labor, long hospital stay in NICU, and increased oxygen level from the use of continuous positive airway pressure.[70]

A meta-analysis emphasizes that this gut dysbiosis precedes the development of NEC in preterm infants, and is characterized by an increase in *Proteobacteria* and a decrease in *Firmicutes* and *Bacteroidetes*.[71] This evidence also supports the notion that administration of early and aggressive nutrition do not increase the incidence of NEC in preterm infants.[72,73]

Infection

The immune system of preterm infants is immature compared to term infants. On the outside, the stratum corneum is thinner, makes them vulnerable to skin infection. On the inside, preterm infants have immature epithelial barrier and smaller pool of monocytes as well as neutrophils with impaired ability to kill pathogens. As a consequence, cytokines are produced in lower quantities which then limit T cell activation and reduce the ability to detect viruses in cells and fight bacteria.[74,75]

Therefore, preterm infants have an increased risk of any kind of infection, especially of late-onset sepsis occurring after three days of age. The risk of infection is increased with the presence of other complications such as prolonged hospitalization (especially due to intubation and intravascular access), bronchopulmonary dysplasia, PDA, and NEC.[76] In very preterm infants, neonatal sepsis is associated with an increase risks for neurodevelopmental impairments, e.g., cerebral palsy and neurosensory deficits.[77] Ocviyanti et al. reported that 58.4% of preterm neonates suffered from neonatal sepsis and 20 of those died of sepsis in a tertiary referral hospital in Jakarta, Indonesia.[78]

Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy unique to preterm infants with an incompletely vascularized retina. The risk

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of ROP and its severity increase as the GA or birth weight decrease. Other factors associated independently with higher rates of ROP may include anemia, high blood transfusion volume, low caloric intake, hyperglycemia and insulin therapy, breathing difficulties, and overall poor health as indicated with lower Apgar score.[79] Mild ROP may resolve spontaneously in the majority of infants without any sequelae.[80] However, infants with severe, untreated ROP are at increased risk of vision impairment and blindness.[79] The incidence of ROP was 6.7% in 2016-2017. This incidence is comparable to the incidence of ROP in high-income countries. However, the mortality rate was 24% which was higher than that in high-income countries.[81]

Hyperbilirubinemia

Elevated total serum/plasma bilirubin is found in almost all preterm infants less than 35 weeks gestation. The main complication of this condition is bilirubin-induced neurologic dysfunction (BIND). This condition occurs when circulating bilirubin is able to cross the blood-brain barrier and binds to the brain tissue. The acute and reversible form of BIND is acute bilirubin encephalopathy (ABE), while the chronic form is kernicterus. The latter is associated with permanent brain damage that may cause intellectual disabilities.[82] Nurani et al. reported that 23% of preterm neonates suffered from hyperbilirubinemia in a tertiary referral hospital in Bandung, Indonesia. Compared to term neonates, preterm neonates are more likely to suffer from bilirubinemia with late onset.[83]

Anemia of prematurity

All infants would experience a physiologic decrease in hemoglobin concentration after birth. But in preterm infants, the process occurs earlier and is more pronounced in its severity compared to their full-term peers.[84] Puspitasari et al. reported that 6% of preterm infants suffered from iron deficiency anemia with median hemoglobin level of 8.4 g/dL, median serum iron level of 48 µg/dL, and median ferritin level of 17%.[85]

Glucose abnormalities

Abnormalities in glucose metabolism may result in neonatal hypoglycemia or hyperglycemia. Preterm infants are especially vulnerable to both conditions owing to their lack of metabolic reserves and associated comorbidities.[86,87] Hypoglycemia is more common in preterm infants in Indonesia. Lubis et al. reported that 26% of preterm infants were hypoglycemic with low birth weight and younger age as associated factors.[88]

Extrauterine growth restriction

Extrauterine growth restriction (EUGR) is prevalent in extremely preterm infants. It is defined as weight, length, or head circumference that are less than 10th percentile at a given t-time, or as >1 SD weight loss between birth and a given t-time. The given t-time can be 36 weeks' PMA or age at discharge.[89,90] Due to physiological adaptations, weight loss in the first 3 weeks (21 days) after birth is still considered normal. However, after this point of time until 42 weeks' PMA, weight loss should no longer occur. A study by Hendrarto et al. in a women and children hospital at Jakarta, Indonesia reported the incidence of EUGR of 43% among 128 preterm infants. It was concluded that human milk is the best nutritional intake for preterm infants although preterm infants with HMF and formula did not have different growth velocity than those human milk.[91]

Long-term complications

Frequent hospitalizations

The number of hospitalizations increases with decreasing GA. Preterm birth was also associated with increased likelihood of hospitalization up to 6 years of age.[92,93] The risk of rehospitalization persists throughout childhood and adolescence in preterm survivors with very low-birth-weight, especially those with history of severe neonatal morbidities.[94] In Indonesia, preterm neonates are usually hospitalized and become the major proportion of NICU population. A study by Leksomono et al. reported 238 preterm infants with very low birthweight hospitalized in a tertiary referral hospital in Yogyakarta, Indonesia from 2011 to 2016. Most of the infants suffered from sepsis with median length of stay of 33 days. Preterm infants might need frequent hospitalizations due to various comorbidities and very low birthweight.[95]

Neurodevelopmental disabilities

Preterm infants are more likely to have intellectual and developmental disabilities, that may emerge later in childhood. Survivors may exhibit motor deficits (cerebral palsy, fine or gross motor delay), sensory impairment (loss of hearing and/or vision), impaired cognitive skills resulting in learning and communicating difficulties, and behavioral and psychological problems.[40,77,96,97]

Chronic medical conditions

Compared to full-term children, higher rates of chronic health issues (e.g. cerebral palsy, asthma poor motor skills, and psychiatric conditions) are seen in preterm children.[98,99] In survivors, prematurity has a potential impact on adult health. Such impact are higher blood pressure, increased insulin resistance, and lower reproductive rate in preterm adults.[100,101] As these neurodevelopmental and chronic health issues are associated with gut dysbiosis in preterm infants. Nutritional management is important to prevent the progression of diseases. Human milk oligosaccharides (HMOs) are one of nutritional interventions which can be considered to overcome the problems.[102]

MANAGEMENT FOR PRETERM INFANTS

Optimizing the outcome of preterm infants

Preterm infant morbidity and mortality can be reduced through timely interventions for the mother and the preterm infant. Maternal interventions are given before or during pregnancy and at delivery,

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whereas appropriate care for the preterm infants should be initiated immediately after birth. The main goal is to prevent potential complications of preterm birth and optimize neonatal outcomes without residual disability.[6]

Maternal interventions

Maternal interventions consist of primary prevention, secondary prevention, and tertiary prevention.[6] Primary prevention is directed to women prior to and during pregnancy. This includes preconception care (education, public and professional policies), proper nutrition and supplementation, smoking cessation, and routine antenatal care with four visits in minimum. Inadequate maternal nutritional intake is associated with preterm births. Deficiencies of calcium, vitamin D, and zinc have been reported to predispose pregnant women to preterm labor. Maternal malnutrition can affect the infants' outcome in term of growth, immunity, development, cognitive skills, cardiovascular system, pulmonary system, and metabolic system. Therefore, multiple micronutrient supplementation is recommended for pregnant women, especially those at risk of preterm labor.[103]

Secondary prevention aims to eliminate or minimize the risk in pregnant women with known risk factors. This includes screening for and management of chronic diseases, such as diabetes and hypertension, behavioral changes for lifestyle risks, administration of pregestational agents, and cervical cerclage. Tertiary prevention aims to improve preterm infants' outcomes after birth. This includes provider education to promote appropriate timing of preterm birth as indicated (induction and caesarean), appropriate management for preterm labor with tocolytic agents in the attempt to slow labor, antenatal administration of corticosteroids to assist lung maturation, and antibiotics administration for preterm premature rupture of membrane (PPROM).[6]

Intervention for preterm infants

The evidence-based intervention for preterm infants include the following:[6] (1) Essential care for all infants, including cord hygiene and proper skin care, thermal care (warming, drying, delayed bathing, skin-to-skin contact), early breastfeeding initiation and exclusive breastfeeding, resuscitation for infants who do not breathe at birth; (2) Additional care for small infants, including Kangaroo Mother Care for infants weight less than 2,000 g at birth, extra feeding support; and (3) Management for preterm infants with complications: management of infants with infection, supportive care for RDS and safe oxygen management, treatment for significant hyperbilirubinemia, hospital care for preterm infants with RDS; including the use of surfactant replacement therapy and/or CPAP, intensive neonatal care. In order to improve the outcomes of preterm infants, interventions should be carried out in conjunction with the obstetrician because it is very dependent on the health and preparation of the expectant mother.

Nutritional management for preterm infants

Preterm birth is a nutritional emergency,[104] as it is essential for the growth and development, establishment of immunity, and metabolism in preterm infants. In particular, those with low birth weight.[105] Poor nutrition has been associated in previous studies with poorer brain growth, that in turn resulted in poor mental skills and psychomotor development.[30] Impaired weight gain and growth in preterm infants are also associated with poor neurodevelopmental outcomes in later life and increased cardiovascular and diabetes risk in adulthood.[106]

On the other side, adequate nutrition in the first weeks after birth in very low-birth-weight infants have been associated with better language score[107] and increased developmental quotient in infants born at less than 28 weeks.[108] Higher energy and protein intake during the first week after birth in ELBW infants is associated with lower risk of growth retardation and higher mental development index scores at 18 months after birth.[109] These facts support the importance of early, aggressive nutritional management in preterm infants, particularly in LBW and VLBW infants.[73]

Human milk as the primary choice of nutrition

Human milk has been known to stimulate the maturation of gastrointestinal tract, gut microbiota, and immune system, which altogether promotes organ development and postnatal growth.[110] For preterm infants, human milk is a source of nutrition for growth and an approach to survive and prevent the complications of prematurity. Studies showed that breastfed preterm infants are less likely to develop NEC, nosocomial infection, retinopathy of prematurity, late-onset sepsis, and cognitive impairment compared to formula-fed infants.[111] Human milk may also be protective against allergic diseases,[112] as well as type 2 diabetes mellitus and cardiovascular disease, later in life.[113]

Human-milk oligosaccharides promote immune development of infants

Human milk also contains HMOs. This is one of many bioactive compounds found in human milk that benefits immunity.[114,115] HMOs are complex soluble glycans synthesized from lactose in the mammary gland and exist in an incredible structural diversity.[116,117] HMOs are available in high concentrations in human milk, ranging from 15-23 g/L in colostrum and 1-10 g/L in mature milk.[111,117] Research has shown that it confers direct and indirect effect on infant systemic and mucosal immune function.

In general, HMOs directly affect the immune system through three mechanisms. First, HMOs can inhibit microorganism adhesion to the intestinal mucosa. They inhibit bacterial and viral infections by binding the pathogen in the lumen or by hampering binding of pathogen to glycan receptors on the cell surface. The latter may occur due to HMOs structural similarities to cell-surface glycan used by microbes.

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Second, HMOs can inhibit inflammatory genes expression. Administration of HMOs has been known to decrease inflammatory cytokine protein levels (among others are IL-8, IL-6, IL-1β) while at the same time increasing the concentration of cytokines involved in homeostasis and tissue repair.[118] HMOs also influence the expression of several chemokines, cytokines, and cell-surface receptors involved in the maturation and development of intestinal immune response.[119] HMOs may also act systemically, as one percent of them are absorbed into the blood and entered the systemic circulation.[116]

Indirectly, HMOs affect immune development by promoting the establishment of gut microbiota. In this case, HMOs act as prebiotics that promote the healthy bacteria growth, including *Bacteroides* and *Bifidobacterium species* that commonly colonized breastfed infants.[116,120] In turn, these bacteria produce short-chain fatty acids (SCFAs), an important energy source for enterocytes and are essential in the maintenance of gut health.[116] In addition, HMOs can influence the signaling pathways of the mucosa in the gut which will contribute to the maturation of enterocytes. One of the HMOs' constituents, 2'-fucosyllactose, is known to suppress proinflammatory signaling pathway which is induced by *Escherichia coli.*[118]

Mechanism of HMO in promoting infant's growth is still being studied. However, available evidences show that HMOs promote infant's growth through microbiota-dependent increased utilization of nutrients for anabolism.[121] HMOs are also known as prebiotics as they become substrates for *Bifidobacteria* which increase the growth of these bacteria. The bacteria will express sialidases or fucosidase which will cleave Fuc or sialic acid (Sia). This end-product can be utilized with other bacteria who cannot utilize HMOs with Fuc or Sia.[122] Brain development is also influenced by HMOs. Sia level was higher in breastfed infants than infants getting formula. High Sia level is associated with good learning, behavioral, and cognitive skills. As Sia is abundant in HMOs and has good bioavailability, it can be absorbed through the intestines.[123]

Challenges in providing preterm human milk

However, the different composition of human milk in preterm delivery makes meeting nutritional needs in preterm infants a challenge. The estimated nutritional requirements of the preterm infant are defined as nutrients needed to support the rates of nutrient accretion and in utero fetal growth in the third trimester of pregnancy. In preterm human milk, the amount of protein and essential minerals such as sodium, calcium, and phosphate is insufficient to meet these needs.[124] And compared to term human milk, the HMOs composition in preterm human milk tends to fluctuate over the course of lactation.[111]

Sustaining the production of human milk is another challenge since many mothers of preterm infants may not be able to breastfeed directly. Poor sucking-swallowing reflex in preterm infants makes them unable to effectively breastfeed for up to months after birth. As a consequence, mothers must learn to assist milk production by expressing human milk. They require substantial support to sustain exclusive breastfeeding both in the hospital and at home.[124]

Overcoming these challenges may require alternatives in the case of inadequate supply of human milk. Donor human milk might offer some benefits despite not as good as the mother's own milk.[125] Other choices are fortification of the mother's preterm human milk with additional nutrients or using a preterm formula.[124,126] Preterm infants with donor human milk had less incidence of feeding intolerance, sepsis, BPD, and NEC compared to those with formula milk.[125]

Prebiotics and infant immunity

One of the additional nutrients often found is synthetic, plant-based oligosaccharides, such as fructo-oligosaccharides (FOSs) and galacto-oligosaccharides (GOSs). These products are supplemented into human milk and infant formula in the attempt to mimic the role of HMOs as prebiotics.[111]

How prebiotics affect infant immunity can be explained by several mechanisms. Prebiotics directly inhibit adhesion of pathogens to the gut epithelium. Therefore, it prevents colonization and infection of pathogenic microbes in the intestinal lumen. Other beneficial effects of prebiotics on immunity are indirectly mediated by regulation of the gut microbiota. Colonization of beneficial bacteria will prevent diarrhea or constipation, positively influence lipid metabolism, and stimulate mineral adsorption. It will also increase the production of SCFAs, such as propionate, acetate, and butyrate by gut microbiota, which is a source of energy for enterocytes.[127]

Furthermore, supplementing preterm formula with prebiotics mixture of short-chain galacto-oligosaccharides (GOS)/long-chain fructo-oligosaccharides (FOS) in a 9:1 ratio was associated in previous studies with better gastric motility and increased in bowel movements. Both effects are important in promoting intestinal tolerance to enteral feeding.[128] However, despite safe and provide significant increment in growth of beneficial bacteria, supplementation with prebiotic did not decrease the incidence of NEC, late-onset sepsis and time to full enteral feeds.[129] A study by Srinivasjois et al. reported that prebiotic supplementation (FOS/GOS and inulin) is safe and tolerated well by preterm infants. Various studies reported different dose administration ranging from 0.8 – 1.5 g/dL with superior outcomes in preterm infants getting dose of 1 g/dL.[129] On the other hand, the role of prebiotics in supporting growth and development of preterm infants is still controversial. Further studies are necessary to establish the mechanism on how prebiotics improving growth and development of preterm infants.[130] To date, there has been no consensus or guidelines on administration of prebiotics for preterm infants both in Indonesia and worldwide.

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Enteral versus parenteral feeding

Early enteral feeding has been associated with improved feeding tolerance, gastrointestinal motility and growth, restoration of gut microbiota, decrease hyperbilirubinemia by promoting stooling, decrease cholestasis, and decreases osteopenia due to more phosphorus and calcium in enteral than parenteral feeding. It also has the potential reduce the occurrence of late-onset neonatal sepsis and NEC.[104,131]

Accordingly, enteral feeding should start as soon as possible after birth. This means giving maternal colostrum immediately after birth and moving to maternal milk as soon as it is available. In some cases, parenteral feeding may be essential, but should not be used as a substitute for enteral feeding and nutrition in the long run.[104] Indications for enteral feeding include preterm infants who have swallowing/sucking dysfunction, good respiratory rate, and insufficient intake while the contraindications are gastrointestinal blockage, NEC, severe respiratory distress, multiorgan failure with high inotropic needs, and hemodynamic disturbances.[132] As for parenteral feeding, the indications are preterm infants with severe gastrointestinal abnormalities, severe asphyxia, congenital heart diseases affecting visceral vascularity, and umbilical flow abnormalities during pregnancy. Parenteral feeding should not be administered for preterm infants with acute liver failure, acute renal failure, dehydration, also persistent electrolyte and metabolic imbalances.[133] Delayed enteral feeding and prolonged parenteral feeding would increase the risk of metabolic complications and infection that compromise growth and development.[134]

Expected weight gain in preterm infants

A few studies reported growth velocity that ranges from 18.3 g/kg/day in 32 weeks' gestation and a minimum of 5 g/kg/day at around 50 weeks, with the administration of 80 mL/kg/d of fluid (5–10% dextrose) on first day of life with 10–20 ml/kg/day daily increments.[135,136]

Summary and recommendations

Some specific recommendations have been made regarding nutritional management of preterm infants which is shown in Table 1.

Table 1. Recommendations for Nutritional Management In Preterm Infants

No.	Recommendation
1.	Early enteral feeding is safe and is preferred compared to parenteral nutrition.
2.	Parenteral feeding may be required to supplement enteral feeding in some cases. However, prolonged use should be avoided due to its complications.[104,134]
3.	Fast, early, or continuous enteral feeding provides better outcomes when compared to slow, late, or intermittent feeding.[134]
4.	Human milk is the best food for all infants but requires supplementation to produce and sustain growth in preterm infants.[104,124,134]
5.	Expressed human milk may be supplemented with fortifiers to meet the high protein requirements of preterm infants without increasing the osmolality of the milk.[134]
6.	Donor human milk can be considered in the absence of adequate supply of human milk.[125]
7.	Providing at least 70 (intravenous) to 90 (enteral) kcal/kg/d calories (glucose and lipids) and 3-4 g/kg/d amino acids/protein may approximate fetal protein accretion and growth in healthy very/extremely preterm, LBW/ELBW infants. Lack of amino acids/protein could lead to neurological deficits.[104]
8.	In very preterm infants (<32 weeks gestation), parenteral nutrition should be started within the first 24 h after birth. This group requires aggressive nutrition, especially regarding protein intake. Pay attention to the protein/energy ratio as excess of amino acids (protein) and energy (glucose, lipids) do not enhance and may harm development.[104]
9.	The role of probiotic and prebiotic supplementation is controversial for NEC cases; however, they may improve the composition of gut microbiota and promote feeding tolerance.[129,137,138]
10.	Feeding of preterm infants can be continued while on continuous positive airway pressure or ventilator.[134]
11.	Optimalization of weight gain in preterm infants helps prevent long-term cardiovascular complications.[134]
12.	Checking for sucking-swallowing ability and optimal weight of preterm infants is important and should be performed prior to discharge from the hospital.[134]
13.	Appropriate counseling and regular follow-up and monitoring promotes better long-term health outcomes.[134]

CONCLUSION

Preterm infants have significantly higher morbidity and mortality rates than term infants with various health complications. Proper prevention measures for maternal and the preterm infants are important. Essential care of the preterm infants and early aggressive nutrition should be provided to support rapid growth that is associated with improved neurodevelopmental outcomes. However, nutritional requirements should be individually adjusted and given at the right time with the appropriate composition. In the end, the goal is not only about survival but making sure that these preterm infants grow and develop without any residual morbidity.

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