

## ***Pertumbuhan dan Perkembangan Bayi Prematur: Apa Saja Risiko Jangka Panjangnya?***

### **Growth and Development in Preterm Infants: What is The Long-Term Risk?**

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#### **ABSTRAK**

**Latar Belakang:** Indonesia menduduki peringkat kelima dalam jumlah kelahiran prematur. Bayi prematur rentan terkena berbagai komplikasi sebagai akibat dari sistem imun yang belum berkembang, sehingga memengaruhi tumbuh kembang bayi tersebut dan memberikan efek jangka panjang hingga dewasa kelak. Komplikasi tersebut dapat dihindari dengan memenuhi kebutuhan gizi bayi prematur.

**Tujuan:** Artikel ini bertujuan untuk menjabarkan karakteristik bayi prematur dalam aspek tumbuh kembang, efek jangka panjang pada perkembangan, dan efek dari imunitas serta kesehatan pencernaan dari bayi prematur dalam mendukung pertumbuhan dan perkembangannya.

**Metode:** Narrative review ini menggunakan artikel sumber primer terbaru dalam 10 tahun terakhir dari PubMed.

**Ulasan:** Laju dan kemampuan bayi prematur dalam mengejar pertumbuhannya bergantung pada berat dan usia lahirnya, di mana semakin rendah berat dan usia kelahiran bayi, semakin lambat pula laju pertumbuhannya. Bayi prematur memiliki struktur otak yang berbeda dengan bayi cukup bulan dan memberikan beragam manifestasi klinis termasuk perubahan jangka panjang pada perubahan emosi, perilaku, kemampuan kognitif dan fungsi eksekutif. Sistem imun yang imatur pada bayi prematur mengurangi proteksi dari sistem imun bawaan maupun adaptif terhadap patogen dibandingkan bayi cukup bulan, termasuk prematuritas komponen mikrobiota pada pencernaan yang memengaruhi penyerapan gizi dan kemampuan kejar tumbuh kembangnya secara langsung. Pemberian gizi yang sesuai dan adekuat terbukti memberikan efek yang positif terhadap pertumbuhan flora normal pada sistem pencernaan, sehingga mampu menyerap gizi secara optimal, sehingga dapat mendukung perbaikan laju tumbuh dan kembang bayi prematur.

**Kesimpulan:** Pertumbuhan dan perkembangan bayi prematur yang optimal didukung oleh pemberian gizi yang cukup yang mendukung pertumbuhan mikrobiota saluran cerna, sehingga mampu mendukung proses kejar tumbuh kembang sekaligus maturitas sistem imun.

**Kata kunci:** bayi prematur, pertumbuhan pada bayi prematur, perkembangan bayi prematur, kesehatan saluran cerna, sistem imun, prebiotik, gizi

#### **ABSTRACT**

**Background:** Indonesia comes in the fifth for the greatest number of preterm births. Preterm infants may inflict various complication as the result of underdeveloped immunity, affecting their growth and development in the long run until they reach adult phase. Such complications could be prevented through adequate nutrition fulfillment.

**Purpose:** This article aimed to elaborate the characteristics of growth and development of premature babies, long term effect on the development and the impact of immunity and gut health of preterm infants in supporting their growth and development.

**Methods:** References cited in this article were obtained from the latest primary literature within the last 10 years.

**Discussion:** The rate and ability of infants to perform catch-up growth depends on the birth weight and gestation age, at which the lower birth weight and lower gestational age had slower rate. Brain structures that of preterm infants differ compared to the term, and these changes give rise to various clinical outcomes, including long term emotional, behavioral changes, cognitive and executive functioning. Immature immune system in preterm infants reduces the protective ability by innate and adaptive immunity in overcoming pathogens compared to term infants, including gut microbiota prematurity which affects nutrition absorption and growth and development catch up ability. Appropriate and adequate nutrition supplementation has shown beneficial effects in promoting the growth of normal gut flora, which allow better absorption of nutrition and therefore enhancing growth rate and supporting the development of preterm infants.

**Conclusions:** Optimal growth and development of preterm infants are supported by sufficient nutrition supplementation to support the growth of gut microbiota, facilitating the catch-up growth and development of premature infants and immune system maturity.

**Keywords:** Preterm Infant, Infant Growth, Infant Development, Gut Health, Immune System, Prebiotics, Nutrition



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## INTRODUCTION

Fifteen million babies are estimated to be born prior to 37 weeks of gestation every year in Indonesia. Currently, Indonesia comes in the fifth place for the greatest number of preterm births, with almost 700,000 preterm babies are born each year and 10.2% of all birth are born with low birth weight (LBW).<sup>1</sup> Preterm birth also contributes about one million death in children under 5 years old and the rest of survivals may suffer from lifelong, detrimental complications that could affect their growth and development.<sup>2</sup>

Preterm babies are further categorized according to its gestational age into extremely preterm, very preterm, and moderate to late preterm, with each of age group span between less than 28 weeks, 28-32 weeks, and 32-37 weeks, respectively.<sup>2</sup> Given the incomplete growth and development in utero, preterm infants are exposed to various insults extra utero that may inflict various complications, one of which is due to underdeveloped immunity. The possible complications are divided into short- and long-term complication. Defective respiratory system, temperature, and glucose regulation, as well as jaundice, feeding difficulties, infection, intracranial hemorrhage, and periventricular leukomalacia are some of the short-term outcomes that may arise from preterm infants. In the long run, they could undergo several hospital readmissions and develop neurodevelopmental and neurobehavioral problems.<sup>3</sup> These complications are both the single largest cause of death among neonates and second most prominent cause of death for children under 5 years old,<sup>4</sup> therefore interventions must be adequately planned and administered to ensure their proper growth and development.

Adequate and appropriate nutrition administration greatly contributes to the ability to perform catch-up growth and development, nevertheless the immature gastrointestinal system poses another challenge in conducting so. The underdeveloped anatomy, physiology, and population of gut microbiota impede the process of nutritional fulfillment, which eventually support the ability to prime the immune system and perform catch-up growth. Therefore, extensive studies have been carried out to find causation relationship between prematurity and the role of nutrition supplementation in achieving proper growth and development catch-up rate.

## METHODS

References cited in this narrative review were obtained from PubMed on the topics of prematurity, growth and development, immunity, and gut health. The author only refers to the most recent articles published in the last 10 years for each topic.

## DISCUSSION

### The Impact of Preterm Birth on Child's Growth

One of the main goals of intervention to the preterm infants is to achieve growth rates that also achieved by infants of similar gestational age in the womb by fulfilling their nutritional requirements.<sup>5</sup> Nevertheless, most preterm infants were unable to meet the needs and reach this rate, causing significant underweight upon hospital discharge. Numerous causes contribute to the inappropriate growth, or growth restriction, and it was mainly determined by three main features of pregnancy, which are the mother, the placenta, and the fetus. While the oxygen and nutrient delivery to placenta are orchestrated by maternal physiology, the placenta plays an important role in consuming up to 35% of the oxygen and glucose extracted from uterine circulation. As the consequences of impaired systems, infants born with growth restriction (intrauterine growth restriction/IUGR) have increased risk of chronic lung condition and other complicating comorbidities in the short term, prohibiting them from effectively consuming liquids through enteral feeding and further aggravating the growth impairment.<sup>6</sup>

According to their birthweight, newborn infants are categorized into small-for-gestational-age (SGA) or appropriate-for-gestational-age (AGA). Infants with preterm SGA are predisposed to IUGR and nutritional deficit, which may continue even after several weeks postnatal, causing impaired growth rate.<sup>7</sup> Several contributing factors to this condition are metabolic and gastrointestinal immaturity, compromised immune function, and other perinatal comorbidities including respiratory problems, anemia, patent ductus arteriosus (PDA), neonatal sepsis and necrotizing enterocolitis (NEC). The frail features with thin, subcutaneous fat layer cause higher basal metabolic rate, as the result of hypothermic stress and higher energy reserve loss. Therefore, SGA infants may develop intrauterine chronic hypoxia due to inability to adapt and utilize energy ineffectively, leading to low survivality.<sup>7,8</sup>

Poor postnatal growth signifies the inability to meet the protein-caloric requirement of constantly growing neonates, leading to the infant growth arrest when they supposed to follow an intrauterine growth pattern.<sup>9</sup> Some growth parameters that are failed to be met by infants with growth failure including time needed to reach optimum daily intake (120 kcal/kg/day), time needed to reach full feeding, time needed to regain birth weight, and weight velocity. A study conducted in Indonesia showed that SGA and respiratory distress were able to predict early growth failure in preterm VLBW infants.<sup>7</sup> Inability to meet this nutrition need during early postnatal life is correlated to long-term health, including impaired childhood neurodevelopment.<sup>6,9</sup> Infants need to



undergo catch-up (rapid/compensatory) growth, usually within the first year of life, facilitated by adequate nutrition to achieve the targeted reference of normal preterm- or term-born infants.<sup>10,11</sup>

The ability to perform catch-up growth (CUG) in the preterm infants allows them in achieving normal height and weight, depending on the birth weight and its correlation to gestational age (AGA or SGA). It is found that nearly 50% of VLBW infants achieved normal height at age of 2 years, which were 86% of them previously achieving normal weight one year before. The number increases following the increasing age. When compared to infants with extremely low birth weight (ELBW), the number of children born with VLBW with short stature at 10 years of age is 80% lesser than children born with ELBW cohort at the same age (7% and 35% respectively). These short stature on ELBW at age 2, 4, and 10 years was correlated with SGA with abnormal height and preterm birth before 28 weeks gestation age.<sup>12</sup>

#### Brain Development: Preterm vs Term Infants

Each gestational age demonstrates different profile of clinical risk, with highest morbidity sustained by extremely preterm and very preterm group.<sup>13</sup> Every preterm birth signifies sudden termination of brain development in utero and upon birth, the brain is still undergone fetal stage of development. Critical phase of brain development occurs at the late second and third trimester of pregnancy, whereby increasing cortical surface area, formation of intraneuronal connection, myelination, the growth of dendrites and axon, as well as synaptogenesis took place.<sup>14,15</sup> Whereas synaptic pruning and myelination are more prominent during late gestation and infancy.<sup>14</sup> These phenomena underlie changes in the brain volume and microstructure of all preterm subgroups, which is associated with perinatal morbidities and neurodevelopmental impairment.

Comparative study of brain development between ex utero preterm and in utero infants with matched gestational age emphasizes the different rates at which brain of each groups developed. This study proved that ex utero preterm infant group underwent slower brain growth trajectory, along with reduced brain volume. The reduction occurs in almost every compartment in the brain, including cerebrum, cerebellum, brainstem, and intracranial cavity, which is predisposed by several risk factors including history of dexamethasone administration, presence of extra-axial blood, the length of oxygen support and confirmed sepsis.<sup>16</sup> Preterm birth also alters the shape of gyri and sulci during brain growth through increasing the intensity and sharpness of gyrification. Various factors are hypothesized to contribute to these differences, including differences in homeostatic regulation of the CSF (as the consequence of changes in blood circulation), high intrauterine pressure prior to and during labor, stress hormone release from mother and infants, and postnatal adaptation to extrauterine life (such as dexamethasone administration) may modify the brain development process including gyrification and later head molding.<sup>17</sup>

The brain of very preterm (VP) infants is characterized by brain vulnerabilities, as shown by larger volume of cerebrospinal fluid (CSF), widespread of

smaller cortical grey matter throughout frontal, parietal, and temporal, as well as smaller volume of temporal white matter. Such changes followed pattern of gradient, whereby the VP infants sustain the most damage, less damage for mid preterm (MP) infants and least damage for late preterm (LP) infants.<sup>13</sup> Smaller total brain volume along with smaller volume of cerebellum, hippocampus, and corpus callosum are associated with lower IQ.<sup>18,19</sup> In addition to this, defect in brain structure corresponds to each impairment, namely executive functioning (reduced total brain volume, white matter volume, cerebellar volumes, corpus callosum size), language (white matter volume, corpus callosum size), memory (white and grey matter volume, cerebellar volume, corpus callosum size), motor skills (cerebellar volumes, corpus callosum size).<sup>19,20</sup>

Preterm infants are susceptible to brain injury, given 33% of them sustains some grade of brain injury in form of periventricular leukomalacia, intraventricular and cerebellar hemorrhage, whereas 10% sustains severe brain injury, an uncommon finding among VP infants.<sup>20,21</sup> Severe brain injury correlated with neurodevelopmental impairment such as cerebral palsy, delayed cognitive function, and impaired motor development. Instead, VP infant survivors were found to show small biparietal width (BPW) and increased interhemispheric distance (IHD), signifying insufficient brain growth and large amount of extracerebral fluid due to disproportional impaired brain growth relative to skull growth, respectively.<sup>13,20,21</sup> Other study observing the brain structure in LP infants also found that children born LP have larger volume of CSF than children born full term (FT) at 6-13 years old. Not only these structural changes persist until teenage years and adulthood, but they also implied in various consequences for each structural change.<sup>18,22</sup>

These structural changes on the total brain volume, grey matter volume and white matter volume in preterm infants persisted until adult, despite the continuous brain volume development.<sup>15,20</sup> Cerebellar volume also found to be decreased among their peers who were born at term, which implied in decreased emotional well-being.<sup>20,23</sup> In VLBW-born adults, altered brain structures were correlated with birthweight, as it affect the volume of grey matter, white matter and its tracts, especially at the temporal lobe.<sup>15</sup> These findings highlight the irreversible changes to the brain as the result of prematurity.

#### Long Term Impact of Preterm Birth on Child's Development

Disrupted brain structure as one of the consequences of premature birth contributes to various clinical repercussions, whose sequelae mainly affects child's development.<sup>24</sup> Neurodevelopmental impairment is one of long term, major outcome of failed catch-up growth of the preterm infants.<sup>3,9-11,14</sup> Corpeleijn et al. hypothesized that neurodevelopmental impairment is the consequence of poor growth, yet both conditions are the result of inadequate nutritional intake.<sup>5</sup> This statement is supported by various studies that pointing out the importance of infants' ability to perform catch up grow. Positive outcome on neurodevelopmental domain



is correlated with increasing weight and BMI,<sup>14</sup> as well as increasing head circumference,<sup>25</sup> especially when it is achieved before 12 months corrected age.

The infants' birth weight in relation to gestational age, whether they born as an AGA or SGA, has also been associated with impaired growth and neurodevelopment.<sup>25-28</sup> SGA-born preterm infants were found to experience intrauterine growth restriction (IUGR) and keeping their short and frail figures throughout childhood, as well as correlated with negative outcome on health risk in the long run.<sup>28</sup> On the other hand, growth restriction can also occur following the birth and cause extrauterine growth restriction (EUGR), which also possess similar association to such impairments.<sup>26,29</sup> The ability of performing CUG, especially in SGA cohort, is essential as it correlates with IQ score, school performance, behavioral problems, hence emphasizing the critical role of optimal early nutrition.<sup>10,14,20,26</sup> Preterm infants who were able to perform CUG, regardless of the state that they were born, are able to grow up to the normal grown children although much longer time needed for SGA infants.<sup>11,28</sup>

As aforementioned in the previous paragraphs, prematurity occurs during which in utero brain development is on its critical period. It is during which the volume of brain, both global and regional, expands by three- to fourfold.<sup>21</sup> Hence, any disruption during this period of development will give rise to multidomain brain dysfunction, including general intelligence, attention, executive function, memory, language, and motor skills.<sup>20,30-32</sup> Lower IQ and math scores has also been reported to be found in preterm-born child<sup>6,19,33,34</sup> as well as preterm adolescents.<sup>35</sup> Another study reported that through certain period of training program, white matter of preterm-born child may change through increasing neurite density, reflecting the brain plasticity.<sup>36</sup>

Cognitive skills are acquired through complex process of bidirectional interaction with their environment and the impaired neurodevelopment capability of the preterm infants may lead to cognitive delay.<sup>19,20</sup> Aside from brain developmental disruption, early motor development including quality of general movement may also predict the cognitive skills at least up to 10 years of age.<sup>31,37</sup> Nevertheless, postural control or quality of movement become a better evident of cognitive ability compared to timing of motor development.<sup>31</sup> Some factors that contribute to the motor performance are related to disrupted brain structure, such as are the incidence of periventricular hemorrhage, head circumference, and size of corpus callosum, which later affect development of some motor domains including fine motor, gross motor, and visual-motor integration.<sup>24,38</sup>

Behavioral changes have also become one of the consequences of prematurity which comprise of different entity of psychiatric domains, including internalization (anxiety, depression), externalization (aggression, social skills, impulsiveness), mental health, and temperament. The contribution of lower gestation age and birthweight are believed to play major role as biological risk factors influencing behavioral changes among preterm-born children.<sup>24</sup> Consequently, changes in brain structure takes place, such as reduced cerebellar

volumes.<sup>23</sup>

Prematurity would also affect the mental health status of children-born premature infants and exhibit various consequences. It is reported that adolescent-born would experience difficulty in transitioning from childhood, would encounter more frequent problems at school and would experience anxiety and depressive symptoms.<sup>39</sup> School performance of premature-born children is found to be associated with various variables, such as gestation age at birth, birth weight, and head circumference.<sup>24,35</sup> On the other hand, adults-born preterm were reported to be at higher risk of anxiety or depression by fourfold, act more cautious and shy, which may underlie social difficulties they experience.<sup>40,41</sup>

### **Immunity and Gut Health Contribution in Supporting Growth & Development of Preterm Infant**

Every term newborn is equipped with untrained, elementary form of adaptive immune system and almost fully rely on their mothers' IgG transmitted through placenta during the last three months of gestation.<sup>42-44</sup> Further activation of these immune components needs protein component from mother's milk, leading to initiation of response to gut pathogen through TLR binding and signal transduction. At the same time, gestation governs the innate immune response in newborns and any impaired innate immune response is most probably generated from insults to the in utero developmental process.<sup>42</sup>

Prematurely born infants may not be able to completely develop and generate immature innate immune system, exposing the infants to infection.<sup>43</sup> Early termination of gestation is often elicited by inflammatory processes underlying the premature ripening of cervix, premature rupture of membranes and infection of the ruptured membranes during labor.<sup>45</sup> These events are linked to disproportionate of white blood cells, therefore impairing the response towards pathogens<sup>46,47</sup> and eventually leading to abnormal distribution and pattern of gut bacteria in preterm infants. Various port de entrée further promotes the invasion of microbes in preterm infants with multiple invasive, intercompartment access. With immature immune components, infectious diseases will easily aggravate and cause detrimental effects on vital organs, such as brain and intestine as source of nutrition absorption for the infants.<sup>44,48</sup>

Regulatory cytokines, which initially decreased among preterm infants, would increase within the first week of life as an induced immune response to diverse environmental insults including IgA antibodies, T cells and interleukins specific towards microbial invasion.<sup>45</sup> Environmental agents (normal microflora) initially interact with the immune system through the gut—associated lymphoid tissue (GALT), facilitated by Pathogen Recognition Receptors (PRRs) through recognition of Microbial Associated Molecular Patterns (MAMPs) to achieve mature and balanced Th1/Th2 immune response through repeated exposure to pathogens.<sup>49,50</sup> Maturation of the gut immune system also involve breastfeeding, as it contains varying components of immune system and human milk oligosaccharides (HMOs), a prebiotic component in breast milk. Mothers of preterm infants have varying



composition of secreted IgA (sIgA) and HMO compared to mothers who gave birth to term infants, as an effort to compensate the inadequate immune systems, affect gut microbiota composition and later contribute to gut maturation, respectively.<sup>51-53</sup> If Th1/Th2 balance is not achieved and the polarity tilted towards Th1, immune system would shift towards pro-inflammatory and causes necrotizing enterocolitis (NEC).<sup>54</sup>

Incomplete maturation of the immune systems in preterm infants reduces the protection by leukocytes in combating bacterial and viral invasion compared to term infants.<sup>54</sup> As the in-utero gut development is terminated in premature birth, the physical and physiological properties of the gastrointestinal system are also impaired, including less active digestive enzymes, immature motility functions, limited absorptive capacity and increased gut permeability.<sup>55</sup> Such problems gave birth to the biggest task in fulfilling the nutritional needs. Despite these differences, the parts of immune cell population converge and shares with those belong to term infants, although other populations such as B, natural killers (NK), and dendritic cells (DCs) were found to develop within the first 3 months and reached the phenotype of that of adult. Such events construe the setpoint of which environmental exposures construct the varying human immune system, regardless of each infants' susceptibility towards external insults.<sup>45,49</sup>

Underdeveloped gastrointestinal system in preterm infants allows incomplete macronutrient digestion and absorption, triggering inflammatory reaction upon undigested content in intestinal lumen.<sup>55</sup> Such consequences could possibly impede the growth and development in preterm infants, as suggested by previous studies.<sup>56,57</sup> Gut microbiota as a vital component of digestive system will gradually increase in diversity as infants get older. In digestion process, gut microbiota serves various functions, comprising of (1) aids nutrient absorption through degradation of host-generated compounds (metabolic), (2) supports the structural development of gastrointestinal tract (trophic), and (3) acts as barrier towards pathogens.<sup>58-60</sup> Method of delivery, dietary intake, and gestation age determine the diversification of gut microbiota,<sup>60</sup> hence preterm-born infants who are exposed to hospital environment, invasive medical equipment and devices, antibiotics administration and parenteral nutrition allow invasion of opportunistic pathogens compared to term newborn.<sup>60,61</sup> Gut microbiota in preterm infants would undergo three phases of maturity, addressed as P1, P2, P3. Dominating facultative anaerobes (e.g., *Bacilli*) and low level of microbiota diversity predominantly occur in P1, whereas P2 is characterized by domination of obligate anaerobes (e.g., *Gammaproteobacteria*) and diversifying microbiota, parallel to increasing stool consistency from meconium to normal postnatal stool. P3 phase is when *Clostridia* dominates and focused on fermentation-based metabolism including lactic acid production.<sup>57,62</sup> Progression of each phase is determined by postmenstrual age (PMA), as well as nutritional factors, diuretics, and antibiotics, as a study shows that transition from P2 to P3 occurred around PMA 29-30 weeks.<sup>57,62</sup>

Microbiota transition in accordance with phase and infant growth were found to be related to total

caloric intake and ratio of lipids, proteins, and carbohydrates. Lipid intake is associated with increasing population of *Actinobacteria* and *Proteobacteria*, whereas protein intake with Firmicutes and carbohydrate intake with all three commensal bacteria.<sup>57</sup> P1 microbiota is associated with higher protein proportion, suggesting higher growth rate and transition to P2 when increased protein and lipid.<sup>57</sup> Major population of *Enterobacteriaceae*, *Clostridium*, *Streptococcus*, and *Bacteroides* in P3 contribute to the increasing capacity of infant to digest food and harvest energy.<sup>50,56,63</sup> In other words, extraction of macronutrients increases and becomes more effective as the population of gut microbiota becomes more diverse. Nevertheless, optimal development of gut microbiota may give positive contribution to enhanced growth rate and support development in children through adequate nutrition fulfillment.<sup>50,56,57,60</sup>

## CONCLUSION

Catching up growth and development in preterm infants necessitate adequate fulfillment of nutrition. Subsequently, maturation of brain, gut, and immune system are achievable and at the same time, impeding detrimental and life-threatening complications resulted from immature immune response. In other words, optimal growth and development of preterm infants are supported by optimum nutrition supplementation, facilitated by normal gut flora.

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