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Current approaches to enteral feeding in preterm infants

Preterm bebeğin enteral beslenmesine güncel yaklaşım

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Abstract

Preterm birth is the leading cause of perinatal morbility and mortality in developed countries. In the last few decades, there has been a significant increase in survival rate of preterm infants, especially of very low birth weight infants. Nutrition of preterm infants should result in growth similar to that of normally growing fetuses of the same gestational age. Unfortunately most preterm infants are not fed enough to achieve this objective; as a result, their growth is restricted by term gestation. This extrauterine growth restriction is particularly evident in infants with developing chronic lung disease, severe intraventricular haemorrhage, necrotizing enterocolitis, or late-onset sepsis. In preterm infants enteral nutrition is the preferred mode of support while human milk is the preferred source of enteral nutrition. Breastfeeding is often the first choice due to its advantages to host defense, content of nutrients and digestion advantages, contribution to gastrointestinal function, neurodevelopmental benefits, advantages to the mother, and its role in reducing the risk of necrotizing enterocolitis. Hormones, growth factors, antiviral and anti inflammatory agents in mother's milk reduce the possibility of sepsis and help maintain a healthy intestinal flora as well. However, for healthy growth of preterm infants, human milk needs to be supported with proteins and minerals. Human milk requires nutrient support to meet the protein and mineral needs of a healthy growing preterm infant. If feeding preterm infants with human milk is impossible or extremely limited, donor human milk or cow-milk-based formulas for preterm infants must be used. This review aims to provide current approaches to feeding in preterm infants.

Keywords: Breastfeeding; Enteral Feeding; Newborn; Nutrition.

Öz

Preterm doğum gelişmiş ülkelerde perinatal morbidite ve mortalitenin önde gelen nedenidir. Özellikle çok düşük doğum ağırlıklı bebekler olmak üzere son dekatlarda prematüre bebeklerin hayatta kalma oranında önemli bir artış olmuştur. Preterm bebeklerin beslenmesinde, aynı gebelik haftasındaki sağlıklı fetusun büyüme hızına benzer bir büyüme hızının sağlaması önerilmektedir. Ne yazık ki, çoğu preterm bebek bu hedefe ulaşabilecek kadar yeterli beslenememektedir. Sonuç olarak preterm bebeklerin term bebeklere göre büyümeleri kısıtlıdır. Bu ekstrauterin büyüme kısıtlılığı özellikle kronik akciğer hastalığı, şiddetli intraventriküler kanama, nekrotizan enterokolit veya geç-başlangıçlı sepsis gelişmişbebeklerde daha belirgindir. Preterm bebeklerde tercih edilen beslenme yöntemi enteral beslenmedir ve besin kaynağı olarak da anne sütü tercih edilir. Çünkü anne sütü konak savunmasındaki avantajları, içeriği, besin ve sindirim üstünlükleri, gastrointestinal sistem fonksiyonlarına katkısı, nörogelişimsel yararları, anneye getirdiği avantajlar ve nekrotizan enterokolit riskini azaltması nedeniyle ilk tercih sebebidir. Anne sütünde bulunan hormonlar, büyüme faktörleri, antiviral ve antienflamatuar ajanlar sepsis olasılığını azaltır ve sağlıklı bir bağırsak florasının oluşmasına yardımcı olur. Bununla birlikte preterm infantların sağlıklı büyümeleri için anne sütünün protein ve mineraller ile güçlendirilmesi gerekir. Anne sütü ile beslenme imkânının olmadığı ya da çok kısıtlı olduğu durumlarda, donör anne sütü veya inek sütü bazlı formulalar preterm bebekler için kullanılmalıdır. Bu derleme, preterm bebeklerin beslenmesi için güncel yaklaşımları sunmayı amaçlamaktadır.

Anahtar Kelimeler: Beslenme; Emzirme; Enteral Beslenme; Yenidoğan.

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Nutritional need of the fetus is met from the mother through placenta-umbilical vein until immediately before birth. Catabolic process starts within hours if the infant can not feed, because nutritional support from the mother is terminated with birth. The most appropriate food for term and preterm infants is breast milk which will be given immediately after birth (1, 2). One should aim to give breast milk as soon as possible after birth, while parenteral feeding that will meet the need for energy and protein should be initiated in preterm infants who can not receive full enteral feeding. Enteral feeding should be increased over time as the infant tolerates, while parenteral feeding support should be decreased and stopped (3-6).

Infants should be provided with adequate food in order to realize genetic growth potential. Preterm infants need more nutritional support compared with term infants because of their rapid growth rates, low nutritional storage, and variable absorption capacities due to immaturity of their gastrointestinal systems (7).

Today the opinion recognized for normal growth rate of the preterm infants after birth is that this rate should be similar to that of a healthy fetus at same gestational age. However, most of preterm infants who are born under 29 weeks of gestation develop extrauterine growth retardation (having a weight under 10th percentile according to patient's weight) (8). In a study evaluating 1,660 preterm infants with a birth weight under 1,500 g, 18% of the infants were discharged with a height and weight under 10th percentile, this rate has been seen to reach 90% (9) (Figure 1).

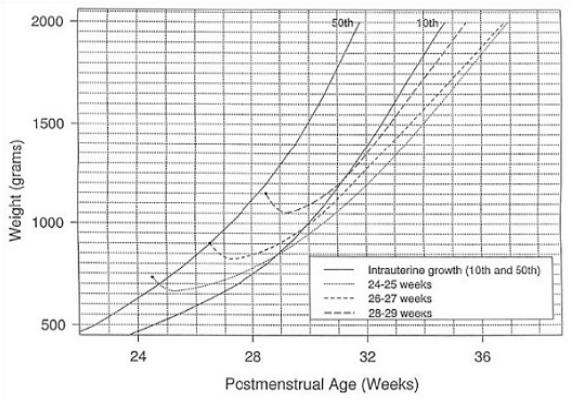

Figure 1. Mean body weight / postmenstrual age of preterm infants between 24 and 29 weeks of gestation (6).

In another study investigating 9,575 preterm infants with a birth weight under 1,500 g; it was found that weight of 79% of the infants fell under normal at the postconceptional week 36 (10). In addition, in another study conducted in 14 centers which evaluated 4,438 preterm infants who weighed between 500 and 1,500 g, 22% of the infants weighed under 10th percentile, while this percentage reached to 97% at the 36th gestational week and to 99% in infants who weighed under 1000 g (11). Common morbidities of preterm infants such as chronic pulmonary disease, serious intraventricular hemorrhage, necrotizing enterocolitis, early and late onset sepsis as well as inability of the infant to receive adequate and appropriate feeding contribute to this extrauterine retardation after birth (12, 13).
There is a significant correlation between growth rate of preterm infants in early neonatal period and growth and neurological development of these infants later in life (14). Therefore, enteral feeding in addition to early total parenteral feeding should be initiated within first days of life in order to minimize adverse motor and cognitive results that may occur in future.

When enteral feeding should be started in preterm infants?

Late start of enteral feeding in preterm infants was the preferred application until short time ago (15). Feeding has been delayed with the concern of necrotizing enterocolitis. However, recent studies and meta-analyses report that it is safe in terms of necrotizing enterocolitis to initiate minimal enteral feeding within first days of life, and to increase feeding with appropriate rates. Studies have demonstrated that delayed enteral feeding may cause mucosal atrophy in the intestines, decreased motility, and digestion-absorption dysfunction due to delayed maturation of the gastrointestinal system enzymes. Furthermore, delayed enteral feeding may lead to attenuation of immune system, abnormal inflammatory response, and increased risk of sepsis by increasing bacterial translocation (16). Infants who can not intake enteral feeding become more susceptible against lung damage, sepsis, neurological damage, and all other pathologies caused by inflammation. Therefore, it is recommended to start enteral feeding from the first day of life regardless prematurity degree of preterm infants (17-19).

How enteral feeding should be initiated in preterm infants?

Although it will meet only a small part of nutritional need, enteral feeding should be started with small amounts as soon as possible in order to increase functional maturation of the immature gastrointestinal systems of preterm infants. Also known as hypocaloric feeding and trophic feeding, minimal enteral feeding is a form of feeding with 10-20 mL/kg/day breast milk or preterm formula within the first days of life. It is important for its trophic effects on the gastrointestinal system rather than providing calories to the infants for growth. It has been shown that minimal enteral feeding accelerates maturation of the gastrointestinal system, prevents mucosal atrophy, and increases intestinal motility and enteric hormone release. In addition, various studies have reported that minimal enteral feeding accelerates shifting to full enteral feeding without increasing the risk for necrotizing enterocolit, shortens duration of hospitalization, increases mineral absorption and bone mineralization (4,20). Umbilical catheterization, mechanical ventilation, apnea or bradycardia attacks, patent ductus arteriosus or the use of indomethacin / ibuprofen that are commonly encountered during treatment and follow-up of preterm infants within

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first days of life are not considered as contraindications for minimal enteral feeding. It is not recommended to dilute breast milk or formula, or to give water at first feeding.

How rate of enteral feeding should be increased in preterm infants?

The amount of enteral feeding is increased considering clinical status of the infant, daily physical examination findings, and status of tolerating minimal enteral feeding. Parenteral feeding is gradually decreased as enteral feeding increases. Although increase rate of enteral feeding varies among centers, considering personal status of each individual patient, it is recommended as 10-35 mL/kg/day (4,21). Table 1 shows a sample feeding plan recommended according to birth weight of preterm infants, and Figure 2 shows the way to be followed in initiation and maintenance of enteral feeding.

Table 1. A recommended nutritional plan based on the birth weights of preterm infants (2).

Birth weight (g)	Feeding frequency	Starting (ml/kg/d)	Amount of increase (ml/kg/d)	Amount of fully enteral nutrition (mg/kg/gün)
<750g	every 2 hours	≤ 10	15	150
750-1000	every 2-3 hours	10	15-20	150
1001-1250	every 2 hours	10	20	150
1251-1500	every 2 hours	20	20	150
1501-1800	every 3 hours	30	30	150
1801-2500	every 3 hours	40	40	165
>2500	every 3-4 hours	50	50	180

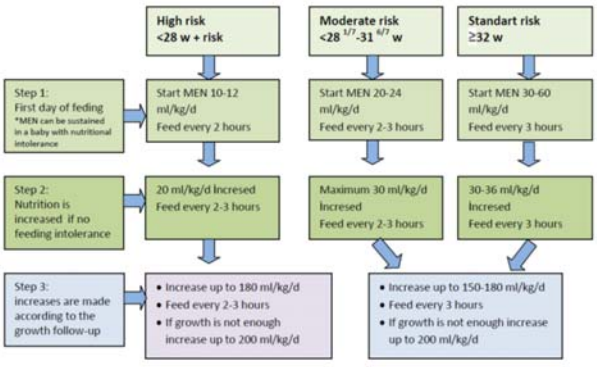

Figure 2. Initiation and maintenance of enteral feeding (2).

Using what and how often enteral feeding should be done in preterm infants?

American Pediatrics Academy, World Health Organization and many nutrition committees stated that the first food of choice in preterm infants should be breast milk from their own mothers. In cases of lack of breast milk from infant's own mother or failure to give infant milk from the mother, the most appropriate food to give to preterm infants has been reported as breast milk from a donor mother. Because breast milk is the food of choice because its advantages in host defense, contents, nutritional and digestive superiorities, contribution of the gastrointestinal system functions, neurodevelopmental benefits, advantages that it brings to the mother, and decreasing the risk for necrotizing enterocolitis. The hormones, growth factors, antiviral and anti-inflammatory agents in breast milk decrease likelihood of sepsis, and help for the formation of a healthy intestinal flora. Therefore, awareness of mothers for importance of breast milk in perinatal and postnatal periods should be increased, and they should be supported for milking (4, 22-24).

Administration of breast milk alone during full enteral feeding, can not meet increased protein, energy, and mineral requirements of the preterm infant. Breast milk enriching additives should be added to breast milk in order to meet increasing and varying nutritional needs of preterm infants and to increase protein and mineral contents of breast milk (25) (Table 2).

Table 2. Nutritional values when using breast milk enricher (2)

	100 ml Human milk	100 ml Human milk + 3 scales human milk fortifier
Protein (g)	1.3	1.9
Fat (g)	4.2	4.5
Carbohydrate (g)	7.0	10
Calories (kcal)	71	86
Calcium (mg)	35	99
Phosphours (mg)	15	59
Magnesium(mg)	2.8	10
Vitamin A (mg)	0.06	0.13
Vitamin C (mg)	3.8	16.3
Vitamin E (mg)	0.35	2.95

Minimal enteral feeding should be done with milked breast milk, after meeting half of the nutrition with breast milk, enriching agents should be added. Another recommendation is to start enriching breast milk after daily enteral intake reach to 100 mL/kg/day. Preterm infants should be fed with preterm formulas when they are lack of breast milk from their own mothers or donor mothers. Preterm formulas have higher amounts of protein, calcium, phosphorus, vitamin and trace elements compared to term infant formulas. Amount of whey proteins in these formulas is close to that of breast milk.
The general view on feeding frequency of preterm infants is once every two hours in infants with a birth weight under 1500 g, and once every three hours in infants with a birth weight over 1500 g (4). However, frequency of feeding can be individualized according to general status, nutritional quality and hypoglycemia status of the infant.

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In what way and how enteral feeding should be done in preterm infants?

Each infant should be individually evaluated considering gestational age, clinical status, and experience of health care staff. Because of uncoordinated sucking and swallowing movements, babies younger than 32-34 weeks of gestation should be fed with orogastric or nasogastric tubes, the feeding process should be performed over 15-20 minutes utilizing the gravity, and no compression should be applied. Orogastric tube should be preferred in infants with respiratory distress, because babies are rather dependent on nasal breathing. However, nasogastric tubes can also be used in infants without respiratory distress because of their easy fixation (26).

Feeding of a preterm infants can be in form of bolus or continuous according to the infant's status. Feeding with bolus form is more physiological in terms of the release of gastrointestinal system hormones. In continuous feeding, lipids, calcium and phosphorus may be given to the infant less than calculated because of sedimentation and adhesion to the tube, and risk of infection may be higher in this case. If continuous feeding will be attempted, it is recommended to put maximum 4-hour breast milk / formula into the pump in order to minimize fat loss. No significant difference has been found between bolus and continuous feeding forms of preterm infants in terms of grow rate, duration of hospitalization, and the incidence of necrotizing enterocolitis (26).

How much food and energy needed for optimal nutrition should be in preterm infants?

Energy and macro/micro foods needed by preterm infants vary depending on birth weight and coexisting diseases. Energy requirement is about 110-135 kcal/kg in a preterm infant, and this need is higher in conditions with increased use of basal energy such as chronic pulmonary disease. It is known that, an energy amount of 120 kcal/kg is sufficient for growth in healthy preterm infants, and more than this amount is known to increase fat deposit in the body. The amount of energy from fat and carbohydrates should be carefully adjusted in ill babies. A carbohydrate rich diet increase energy expenditure, resulting in an increase in production of carbon dioxide. In this case, respiratory rate, oxygen consumption, and workload increase. Insufficient energy intake disrupts the protein absorption. Whereas excessive energy impairs the body composition in favour of fats, Glucose requirement of preterm infants is higher than term infants due to insufficient glycogen storage and gluconeogenesis (27).

36-55% of total energy intake should be provided by fats. Linoleic and alpha-linoleic fatty acids should be present in the diet, because they can not be synthesized endogenously. Medium-chain fatty acids are added to preterm formulas in order to increase fat absorption. Rate of medium-chain fatty acids of the current preterm formulas is 40% to 50%. Positive effects of long-chain polyunsaturated fatty acids on vision and neurological development have been demonstrated. Again nucleotides have potential benefits including intestinal trophic impact, increased growth rate in patients with low birth weight, improvement in immune functions, and increase in the production of long-chain polyunsaturated fatty acids (28, 29).

Everyday, 3% of body protein is lost in preterm infants, and this loss is correlated with the degree of prematurity. Daily protein requirement is estimated as 4.0-4.5 g/kg in preterm infants and particularly in those with a very low birth weight. Well proportioned protein energy intake is important both for utilization of proteins and prevention of fat deposits. The recommended rate is minimum 2.5 g/100 kcal, and maximum 3.6 g/100 kcal (28, 29).

Problems encountered in feeding of preterm infants

Gastrointestinal system intolerance and gastric residue of the premature

Gastrointestinal system intolerance is a commonly encountered problem during follow-up of preterm infants in intensive care unit. Although anatomic development of gastrointestinal system is largely completed in intrauterine week 20, physiologic and histologic maturation of the gastrointestinal system continue especially in the third trimester and postnatal period. It is claimed that gastrointestinal system intolerance of premature infants is caused by enzyme activity and immature nature of the intestinal epithelial cells. Pancreatic lipase and lactase activities of premature infants are lower than those of term infants (30). Although there is no a clear consensus on the definition, gastrointestinal system intolerance can be considered as inability to maintain enteral feeding plan due to abdominal distension and vomiting in the presence of 50% gastric residual volume (31). Gastrointestinal system intolerance should be distinguished from early stage necrotizing enterocolitis in preterm infants. In addition, patients with prolonged gastrointestinal system intolerance should also be evaluated by pediatric surgery department for possible surgical problems. Treatment options in infants with gastrointestinal system intolerance may include non-nutritive sucking (pacifier and/or mother breast), feeding with drip infusion, the use of prokinetic agents such as domperidone and erythromycin, abdominal massage implementation to increase intestinal motility, probiotics, the use of formulas containing enteral insulin and hydrolyzed protein, or amino acid-based formulas (30, 32-35). Evidence level of these recommendations is low and parts of them are based only one a single study.

Gastroesophageal reflux

Gastroesophageal reflux is commonly seen in preterm infants due to several reasons such as back-to-sleep campaign which facilitates leakage of the gastric contents to the esophagus, over nutrition, esophageal motility and clearance insufficiency (36). Gastroesophageal reflux occurring with these mechanisms in these infants is often not considered as pathologic. However, various problems such as aspiration, esophagitis, nutritional problems, and growth retardation may develop in patients with moderate-to-severe gastroesophageal reflux, and treatment options should be considered for these babies (37). Primarily non-pharmacological applications should be considered for the treatment. These include giving to

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the infant face-down and left lateral positions, prolongation of feeding time in non-acid reflux, feeding with frequent low volumes in acid reflux. Hydrolyzed formulas can be useful in acid reflux. Increasing consistency of breast milk or formulas may cause negative outcomes in premature infants (38). Although H_2-receptor blockers, and metoclopramide proton pump inhibitors are widely used in infants with symptomatic reflux, there is no sufficient evidence for safety and effectiveness of these drugs in newborn babies (39, 40).

Necrotizing enterocolitis and short bowel sendrome

Necrotizing enterocolitis is the most commonly seen emergency in neonatal intensive care units. Premature infants account for 90% of all cases with necrotizing enterocolitis, and preterm birth is the most important factor in the etiology of necrotizing enterocolitis (41). The other factors associated with necrotizing enterocolitis include perfusion disruption and mesenteric ischemia, thrombosis, feeding with formula, colonization with pathogenic organisms, vasoactive inflammatory mediators, and genetic predisposition. Intestinal motility and intestinal immunity is insufficient, mucosal defense mechanism is poor, and gastrointestinal system permeability is high in preterm infants. For these reasons, are more susceptible to passing of pathogenic organisms to the circulation with bacterial excessive proliferation, and to the development of necrotizing enterocolitis with an intense intestinal inflammatory response. The incidence of necrotizing enterocolit has been reported as 3.2-14% in infants with a very low birth weight (42, 43). Necrotizing enterocolitis often presents with abdominal distension and tenderness, malnutrition, bloody stool and sepsis findings. The diagnosis can be established with abdominal radiograph findings. Surgical intervention is required in 20-40% of infants with necrotizing enterocolitis, and mortality can reach to 50% in this group of patients (41, 44). In addition, necrotizing enterocolitis may cause serious morbidity including growth retardation, neurodevelopmental disorders, vision and hearing problems, intestinal obstruction, and short bowel syndrome (41).

Necrotizing enterocolitis is the most common cause of short bowel syndrome, which is an important cause of morbidity and mortality in neonatal period, by 35% (45). The incidence of surgical short bowel syndrome has been reported as 0.7% in infants with a very low birth weight. After surgery, following acute phase with excessive fluid and electrolyte losses, residual phase containing adaptation of the gastrointestinal system, reorganization of the villi crypts, functional alterations in nutritional absorption and motility starts. Management of these patients who required prolonged parenteral feeding support is difficult, and requires a multidisciplinary approach (45).

In conclusion; there is a significant correlation between growth rate of preterm infants in early neonatal period and growth and neurological development of these infants later in life. Therefore, minimal enteral feeding with breast milk should be started from the first day of life, while parenteral feeding that will meet the need for energy and protein should be initiated from the first hours even in excessively preterm infants. Awareness of mothers for importance of breast milk in perinatal and postnatal periods should be increased, and they should be supported for milking. Infants should be closely monitored for necrotizing enterocolitis, primarily non-pharmacological treatment options should be tried in cases of nutritional intolerance and gastroesophageal reflux.

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