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# Factors Related to Full Enteral Feeding Achievement in Very Low Birth Weight Infants

## Çok Düşük Ağırlıklı İnfantlarda Tam Enteral Beslenmeyi Etkileyen Faktörler

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## ABSTRACT

**Aim:** Many feeding guidelines recommend early and progressive enteral feeding; however, it is a challenge to feed premature infants due to the immaturity of the gastrointestinal tract and concerns about necrotizing enterocolitis, as well as various comorbidities and nonspecific signs of feeding intolerance. Determining the factors that affect the success of full enteral feeding (FEF) is crucial for improving the nutritional management and short-term and long-term outcomes of very low birth weight (VLBW) infants. The purpose of this study is to evaluate the effect of clinical conditions or feeding-related factors on FEF achievement in VLBW infants.

**Materials and Methods:** A retrospective, single-center cohort study was conducted on preterm infants with birth weight < 1500 g and gestational age ≤32 weeks. Feeding of 10-20 ml/kg/day, preferably with breastmilk, was started from the first day of stable prematurity. The amount of nutrition was increased to 20-35 ml/kg/day. In unstable high-risk babies, minimal enteral feeding was administered for the first 3-7 days, followed by an increase of 20 ml/kg/day.

**Results:** The median time to reach FEF was 13 days (9-18). In univariate analysis, factors associated with longer time to achieve full feeds were preeclampsia, small for gestational age (SGA), delivery room intubation, significant patent ductus arteriosus (hsPDA), late onset sepsis, and formula feeding. Multivariate regression analysis revealed that SGA, hsPDA, and formula feeding were independently associated with longer time to achieve FEF.

**Conclusion:** In our study evaluating VLBW babies, being SGA, the presence of hsPDA, and formula feeding were found to be factors that negatively affected FEF success. Efforts should be undertaken to enhance the nutritional care of VLBW infants, aiming to mitigate potential complications arising from delayed attainment of FEF.

**Keywords:** Nutrition; full enteral feeding; newborn; very low birth weight infants; breastmilk

## ÖZ

**Amaç:** Birçok beslenme rehberi, erken ve aşamalı enteral beslenmeyi önermektedir. Ancak, gastrointestinal sistemin olgunlaşmamış olması, nekrotizan enterokolit korkusu, çeşitli eşlik eden hastalıklar ve beslenme intoleransına ait spesifik olmayan belirtiler nedeniyle prematüre bebeklerin beslenmesi zordur. Tam enteral beslenme (TEB) başarısını etkileyen faktörlerin belirlenmesi, çok düşük doğum ağırlıklı (ÇDDA) bebeklerin beslenme yönetiminin ve kısa/uzun vadeli sonuçlarının iyileştirilmesi açısından önemlidir. Bu çalışmanın amacı, ÇDDA bebeklerde klinik durumların veya beslenme ile ilişkili faktörlerin TEB başarısına etkisini değerlendirmektir.

**Gereç ve Yöntemler:** Doğum ağırlığı <1500 g ve gestasyonel yaşı ≤32 hafta olan prematüre bebekler üzerinde retrospektif, tek merkezli bir kohort çalışması yürütüldü. Stabil prematüritelerde, tercihen anne sütüyle olmak üzere, 10-20 ml/kg/gün beslenmeye ilk günden itibaren başlandı. Besin miktarı günde 20-35 ml/kg olacak şekilde artırıldı. Stabil olmayan yüksek riskli bebeklerde ise ilk 3-7 gün boyunca minimal enteral beslenme uygulandı, ardından günde 20 ml/kg artış yapıldı.

**Bulgular:** TEB'ye ulaşma süresi ortanca 13 gündü (9-18 gün). Tek değişkenli analizde, TEB'ye ulaşmada sürenin uzamasıyla ilişkili faktörler preeklampsi, gestasyonel yaşa göre küçük (SGA) olma, doğum odasında entübasyon, hemodinamik olarak anlamlı patent duktus arteriyozus (hsPDA), geç başlangıçlı sepsis ve mama ile beslenme olarak bulundu. Çok değişkenli regresyon analizinde ise SGA, hsPDA ve mama ile beslenmenin bağımsız olarak TEB'ye ulaşma süresini uzattığı belirlendi.

**Sonuç:** ÇDDA bebeklerin değerlendirildiği çalışmamızda, SGA olmak, hsPDA varlığı ve mama ile beslenme, TEB başarısını olumsuz etkileyen faktörler olarak saptanmıştır. TEB'ye geç ulaşımın neden olabileceği komplikasyonları azaltmak amacıyla, ÇDDA bebeklerin beslenme bakımının geliştirilmesine yönelik çabalar artırılmalıdır.

**Anahtar Kelimeler:** Nutrisyon; tam enteral beslenme; yenidoğan; çok düşük doğum ağırlıklı infant; anne sütü

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## INTRODUCTION

Survival rates of preterm babies are increasing in parallel with the developments in neonatal intensive care. However, short- and long-term morbidities, especially of premature babies with younger gestational age, are increasingly becoming a concern (1). It is well known that adequate nutrition and growth is critical for every premature baby, and especially for those born with a very low birth weight (VLBW) of less than 1,500 grams. The nutritional needs of these infants are extremely high, so it is necessary to provide adequate nutrition to meet their full potential in terms of growth and neurological outcomes (2). Additionally, prematurity-related complications and physiologic immaturity of the gastrointestinal tract affect metabolic energy requirement (3).

Optimal nutritional support is a critical therapy to avoid postnatal growth failure in preterm infants and improves lifelong outcomes such as developmental delay, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) (4-6). Ehrenkranz et al. reported an association between growth velocity and the likelihood of cerebral palsy and neurodevelopmental impairment at 18 months of age (4). Klevebro et al. reported that early energy and protein intakes during the first week of life may reduce postnatal weight loss and risk of morbidities in extremely preterm infants (5). Early and progressive enteral feeding is important because it decreases the need for central catheters, infection risk (7), and length of hospital stay (8). On the other hand, lack of enteral nutrition increases the risk for gastrointestinal dysfunction and necrotizing enterocolitis (NEC) (9,10).

Many feeding guidelines recommend early and progressive enteral feeding (11,12), but it is a challenge to feed these infants because of immaturity of the gastrointestinal function and concerns about NEC, as well as various comorbidities and nonspecific signs of feeding intolerance (13). In addition, hospital-related factors such as low availability of human milk and lactation support influence the preterm nutrition practices. Therefore, determining the factors affecting the success of full enteral feeding (FEF) is important to improve the nutritional management and short- and long-term outcomes of VLBW infants.

The purpose of this study is to evaluate the effect of clinical conditions or feeding-related factors on FEF achievement in VLBW infants.

## METHOD

A retrospective, single-center cohort study was carried out in the neonatal intensive care unit (NICU) of Elazig Research and Training Hospital, a tertiary-level neonatal referral center in Eastern Turkey. Preterm infants with a birth weight of <1500 g and a gestational age of ≤32 weeks who were admitted to the NICU between January 2016 and December 2019 were eligible for inclusion. Infants with congenital malformations or who died within 2 days of life or never received enteral feeding were excluded. The Hospital Ethics Committee approved the study protocol.

Medical charts were reviewed, and the following variables were collected: gestational age, birth weight, sex, perinatal characteristics, neonatal morbidities, use and duration of central catheters, feeding type, timing of enteral feeding, and time to achieve FEF. In our unit, a feeding protocol is carried out in line with the recommendations of the Turkish Neonatal Society (14). Feeding of 10-20 ml/kg/day, preferably with breastmilk, was started from the first day of stable prematurity. The amount of nutrition was increased to 20-35 ml/kg/day. In unstable high-risk babies, minimal enteral feeding was administered for the first 3-7 days, followed by an increase of 20 ml/kg/day. A stable preterm infant was defined as one without significant hemodynamic, metabolic, or respiratory instability, such as hypotension, capillary refill >3 s, severe metabolic acidosis or a worsening respiratory status.

Full enteral feeding is defined as the attainment of at least 150 ml/kg/day in enteral intake. Gastric residual was characterized as bilious or bloody residuals exceeding 50% of the previous feed volume before the subsequent feeding. Antenatal steroids prophylaxis was defined as 1 or 2 doses of betamethasone. Small for gestational age (SGA) was defined as birth weight <10th percentile based on the Fenton 2013 growth chart. Sepsis was defined as clinical or laboratory findings compatible with sepsis.

The primary outcome of this study was the factors related to the time required to achieve full enteral feedings in VLBW infants.

### Statistical analysis

Statistical analysis was performed using the SPSS 22.0 program. Data are presented as median (IQR), and n (%) as appropriate. Pearson correlation coefficient was used to analyse the association between quantitative variables. Categorical data were analyzed using $x^2$ test and Fisher's exact test. Univariate and multivariate COX regression analysis were used to identify the association between risk factors and time to FEF.

## RESULTS

A total of 190 VLBW infants were admitted to our NICU. Ten infants who died within the first two days of life and four who never received enteral feeding were excluded, leaving 176 infants for inclusion in

**Table 1.** Demographic and clinical characteristics of patients

| | |
|---|---|
| **Gestational age, week** | 29 (28-31) |
| **Birth weight, gram**<br>**<1500 gr**<br>**>1500 gr** | 1232.5 (970-1375) |
| **Cesarean delivery** | 129 (73.3) |
| **Male sex** | 90 (51.1) |
| **Apgar score at 1 minute** | 6 (4-7) |
| **Apgar score at 5 minute**<br>**APGAR≤7** | 8 (6-8) |
| **SGA** | 28 (15.9) |
| **Antenatal steroid** | 95 (54.4) |
| **Maternal pre-eclampsia** | 34 (19.3) |
| **PPROM** | 42 (23.9) |
| **Chorioamnionitis** | 10 (5.7) |
| **Gestational diabetes** | 6 (3.4) |
| **Delivery room intubation** | 45 (25.6) |
| **Invasive mechanical ventilation** | 112 (63.6) |
| **Early-onset sepsis** | 23 (13.1) |
| **Hs- PDA** | 49 (27.8) |
| **Late-onset sepsis** | 53 (30.1) |
| **Umbilical venous catheter** | 131 (74.4) |
| **Catheter duration, days** | 10 (7-14) |
| **Necrotizing enterocolitis** | 8 (4.5) |
| **Bronchopulmonary dysplasia** | 42 (23.7) |
| **Retinopathy of prematurity** | 26 (14.8) |

Data are expressed as n (%) or median (Interquartile range) Hs- PDA : Hemodinamically significant Patent ductus arteriozus, PPROM :Preterm premature rupture of membrane, SGA: Small for gestational age

**Table 2. Feeding characteristics of patients.**

| | |
|---|---|
| **First enteral feeding (days)** | 3 (2-3.5) |
| **< 24 hours of life** | 34 (19.3) |
| **< 72 hours of life** | 102 (58) |
| **>72 hours of life** | 40 (22.7) |
| **Type of feeding** | |
| **Breast milk** | 35 (19.9) |
| **Formula only** | 81 (46) |
| **Mixed** | 60 (34.1) |
| **Time of parenteral nutrition (days)** | 10 (6-14) |
| **Time to achieve FEF (days)** | 13 (9-18) |

Data are expressed as *n* (%) or median (Interquartile range) , FEF: Full enteral feeding

the analysis.. Of these infants, 162 (92%) achieved FEF; 4 died after reaching FEF.

In the present cohort of 176 preterm infants, 51% were male (n=90), the median gestational age was 29 weeks (28-31), and the median birth weight was 1232,5 grams (970-1375 grams). Twenty-eight infants (15,9%) were SGA. Forty-five (25,6%) infants had delivery room intubation. Invasive mechanical ventilation was used in 63,6% of infants. Forty-nine infants received treatment for significant PDA. The majority of infants had a central venous catheter (74,4%, n = 131) and the median time was 10 days ( 7-14 days) (Table 1).

Enteral feeding was introduced to 77,2% of patients within the first 72 hours of life. Causes for delay of enteral feeding were absence of maternal milk (n=22), cardio-respiratory distress (n = 6), and biliary or hematic gastric residuals (n=8). Only 19,9% of infants were exclusively maternal milk fed, and 46% of them were formula only fed. Donor human milk was not available in our institution. The median time to reach full enteral feeding was 13 days (9-18) (Table 2). Enteral feeding was withheld during the later postnatal days in 5 infants (2.8%) due to gastric residuals, in 11 infants (6.2%) due to abdominal distension, and in 8 infants (4.5%) due to NEC.In univariate analysis, factors associated with longer time to achieve full feeds were preeclampsia, SGA, delivery room intubation, significant PDA, late onset sepsis (LOS) and formula feeding. Higher gestational age was associated with less time to full feeds. Multivariate regression analysis revealed that lower gestational age, SGA, significant PDA, and formula feeding were independently associated with longer time to achieve FEF (Table 3). PDA was a

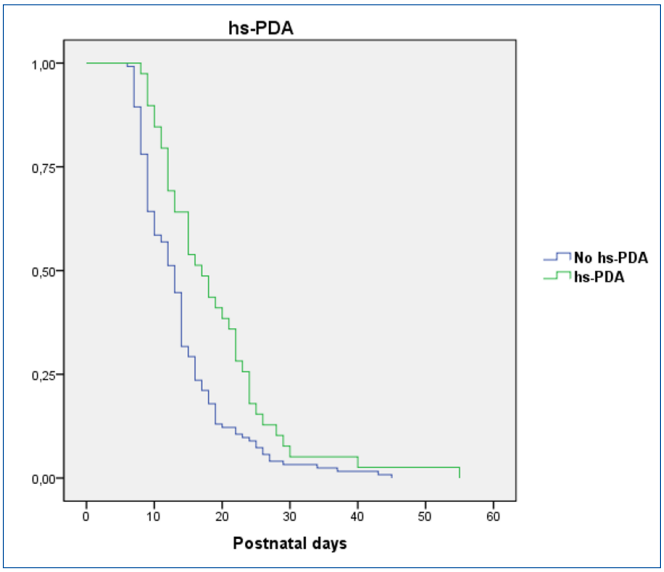


**Figure 1.** Time to achieve full enteral feeds depending on diagnosis of hemodynamically significant patent ductus arteriozus (hs-PDA)

**Table 3.** COX regression analysis for time to achieve full enteral feeding.

| | Univariate model | | Multivariate model | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Gestational age | 1.488 (1.346-1.645) | **<0.001** | 1.398 (1.249-1.564) | <0.001 |
| Apgar score at 5 minute < 7 APGAR≤7 | 0.786 (0.557-1.109) | 0.170 | - | |
| Male | 0.864 (0.632-1.179) | 0.356 | - | |
| Cesarean | 0.887 (0.623-1.265) | 0.509 | - | |
| SGA | 0.596 (0.387-0.916) | **0.018** | 0.568 (0.364-0.886) | **0.013** |
| Antenatal steroid | 1.34 (0.97-1.85) | 0.078 | - | |
| Maternal pre-eclampsia | 0.657 (0.438-0.986) | **0.043** | 0.741 (0.467-1.175) | 0.203 |
| Prolonged rupture of membrane | 0.840 (0.548-1.289) | 0.425 | - | |
| Chorioamnionitis | 0.725 (0.369-1.423) | 0.349 | - | |
| Gestational diabetes | 0.778 (0.343-1.766) | 0.548 | - | |
| Delivery room intubation | 0.699 (0.451-1.083) | 0.109 | - | |
| Invasive mechanical ventilation | 0.816 (0.586-1.136) | 0.228 | - | |
| Early-onset sepsis | 0.764 (0.486-1.201) | 0.243 | - | |
| Significant PDA | 0.369 (0.228-0.597) | **<0.001** | 0.546 (0.371-0.803) | **0.002** |
| Late-onset sepsis | 0.651 (0.462-0.917) | **0.014** | 0.766 (0.539-1.089) | 0.138 |
| First enteral feeding <72 hour | 1.312 (0.914-1.884) | 0.141 | - | |
| Formula only | 0.498 (0.361-0.688) | **<0.001** | 0.556 (0.398-0.775) | **0.001** |

Hs- PDA :Hemodinamically significant Patent ductus arteriozus, SGA: Small for gestational age

significant predictor of time to achievement of full feeds. Infants with a significant PDA received full enteral nutrition at the 16th day (95% confidence interval [CI] 15th–21st), whereas patients without PDA achieved it at the 13th day (95% CI 12th–15th; p=0,003) (Figure 1).

## DISCUSSION

This study aimed to investigate factors related to the time to achieve full enteral feedings in VLBW infants. In our cohort, the median time to FEF was 13 days. Gestational age, SGA, significant PDA, and formula feeding were associated with a longer time to FEF. As expected, the higher the gestational age, the shorter the time to FEF.

Several studies on preterm infants reported that the time to FEF varies greatly between centers and countries. A large-scale study comparing the feeding practices of neonatal units on five continents showed that time to FEF in VLBW infants varies greatly between units (8-33 days) (15). In a retrospective study based on data from the Emilia Romagna Perinatal Network, which includes 9 neonatal intensive care units in Italy, time to FEF was 12.9 days (16). Tewoldie et al. reported a median time to achieve full enteral feeding of 8 days (interquartile range, 7–10 days) in infants with birth weights between 1,000 and 2,000 g, noting that each additional week of gestation was associated with an 18.8% reduction in the time required to reach full feeds (17). Similarly, in our study, we found that greater gestational age was associated with a shorter time to achieve full enteral feeding.a A prospective cohort study of 304 VLBW infants reported 11 days (8-15 days) of time to FEF (18). In the present study, the time to achieve FEF was 13 days. These differences can be attributed to the variability of the study population and also the feeding protocols between units. In addition, other factors such as the availability of human milk and different approaches to feeding intolerance and symptoms of NEC also affect the time to full feeding. It is important to explore the impact of these differences in-unit nutrition protocols on the long-term health and development of infants.

Formula feeding has been identified as a risk factor for increased NEC rates and feeding intolerance. Maternal milk feeding reduces complications such as sepsis and NEC and improves prematurity-related outcomes (19). However, after preterm birth, mothers may not be able to produce enough milk. In case of insufficient lactation support or no donor milk banking, the availability of human milk is difficult. Especially for young babies, it is common to delay starting feedings (instead of starting with formula) until breastmilk comes in. Therefore, the predominant use of formula in nutrition may lead to a slow transition to full enteral nutrition. Corvaglia et al. reported that human milk-fed infants reached full feeding 1.4 days earlier

than formula-fed infants (16). Studies also showed that earlier establishment of FEF with human milk was associated with a lower risk of sepsis in extremely low birth weight infants. In our study, almost half of the patients had formula feed, and only 19% of them had exclusive maternal milk. Consistent with the literature, formula feeding was associated with a longer time to reach FEF. In order to increase breastfeeding, it is necessary to focus on measures such as lactation support and breastmilk banking.

Although there is no consensus on the best approach to provide enteral feedings to a preterm infant, some reports recommend initiating it within the first 24 to 72 hours of life (20,21). In our study, 77% of our patients started enteral feeding within 3 days of life. The reason for the delay in enteral feeding was mostly waiting for breastmilk. A few of them had clinical reasons, such as respiratory or gastrointestinal instability. Vasconcelos et al. reported a longer time to FEF in neonates that started enteral feeding > 72 hours of life (22). However, we did not find a significant relationship between the timing of first enteral feeding and time to reach FEF. This can be explained by differences between study populations.

Significant PDA has been associated with delayed initiation of enteral nutrition and FEF success. Corvaglia et al. (16) reported longer (>4 days) time to achieve FEF in infants with significant PDA. Patole et al. (23) revealed that PDA is a risk factor that prolongs FEF time, independent of gestational age, sepsis, and SGA status. It is well known that significant PDA and its treatment with indomethacin/ibuprofen negatively affect mesenteric perfusion (24). Mosalli et al. reported decreased incidence of NEC following PDA prophylactic surgical ligation in extremely low birth weight infants (25). The longer time to FEF may be a result of clinicians acting more cautiously in infants with PDA. There are different approaches regarding optimal nutrition in VLBW infants with PDA. Research is needed on how to improve FEF success in this group of infants.

Data are controversial regarding the impact of having intrauterine growth retardation (IUGR) on FEF success. Several studies revealed that SGA infants have longer time to achieve FEF (26, 27). Dorling et al. (28) found that infants who had abnormal antenatal Doppler flows were more prone to feeding intolerance. For these reasons, enteral feeding is often delayed, although it is unclear whether it will be beneficial in these babies. On the other hand, Mihatsch et al. reported no difference between IUGR and non-IUGR infants regarding feeding tolerance and FEF achievement (29). A very recent study performed in preterm growth-restricted infants reported that early feeding was not associated with a higher risk of NEC (30). In the present study, SGA was identified as a risk factor for FEF achievement.

Our study had some limitations. Since the single-center sample size was low, generalization of the results may be difficult. Further, data collection relies on keeping accurate medical records, which sometimes results in data being incomplete or other unrecorded factors being overlooked.

## CONCLUSION

In our study evaluating VLBW babies, being SGA and the presence of significant PDA and formula feeding were found to be factors that negatively affected FEF success. Improving feeding approaches in these clinical conditions and supporting practices that will increase breastmilk supply may ameliorate the nutritional management of VLBW infants. No effect of prenatal characteristics on FEF success was detected. Identifying risk factors associated with FEF success may help improve routine clinical management of VLBW infants. Efforts need to be made to optimize the nutritional management of VLBW infants to prevent potential complications resulting from delayed FEF achievement.

**Ethical approval:** Ethical approval was obtained from the Non-Interventional Research Ethics Committee of Firat University prior to initiation of the study

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**Conflict of interest statement:** The author declares no conflicts of interest.

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