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ARAŞTIRMA / RESEARCH

Evaluation of influence of Bifidobacterium lactis and Hindiba inulin on feeding intolerance and weight gain in premature babies

Prematüre bebeklerde beslenme intoleransında Bifidobakteriyum laktis ve Hindiba inülinin beslenme intoleransı ve ağırlık artışı üzerine etkilerinin değerlendirilmesi

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Abstract

Purpose: The aim of this study was to evaluate the influence of Bifidobacterium lactis and Hindiba inulin on feeding intolerance and weight gain in premature babies.

Material and Methods: Eighty nine premature babies with the diagnosis of feeding intolerance were enrolled in the study. Study group had Bifidobacterium lactis (5x109 CFU) + Hindiba inulin (900 mg) (Maflor) per oral, while control group did not have any medication for feeding intolerance.

Results: B. lactis ve H. inulin was continued for a mean of 10 days. Time of full enteral feeding and time of starting oral feeding were longer in study group and this was statistically significant. Although lower birth weight, longer total parenteral nutrition duration, later starting of oral feeding and longer duration for start of full enteral feeding in the study group, there was no statistical difference in weights of the babies at discharge time when compared with the control group. When the groups were compared according to weight gain, study group gained more weight and it was statistically significant. Although necrotizing enterocolitis was not significantly different between groups, babies in the study group diagnosed as in Stage 1 and did not worsen. 33.3% of the babies in the control group progressed to Stage 2.

Conclusion: Probiotics and prebiotics might have positive effects due to higher weight gain especially >1500 g birth weight infants and not advancing necrotizing enterocolitis in the study group having B. Lactis and H. inulin.

Key words: Probiotics, prebiotics, feeding intolerance, premature babies.

Öz

Amaç: Bu çalışmanın amacı prematüre bebeklerde beslenme intoleransı ve ağırlık artışı üzerine Bifidobakteryum laktis ve Hindiba inülini'nin etkisinin değerlendirilmesidir.

Gereç ve Yöntem: Beslenme intoleransı tanısıyla izlenmekte olan 89 prematüre bebek bu çalışmaya alınmıştır. Çalışma grubundaki olgulara Bifidobakteriyum laktis (5x109 CFU) + Hindiba inülini (900 mg) (Maflor şase) oral yolla verilirken, kontrol grubundaki olgulara beslenme intolransı için herhangi bir tedavi verilmedi.

Bulgular: Çalışma grubundaki olgulara B. Laktis ve Hindiba inülinine ortalama 10 gün devam edilmişti. Oral beslemeye başlama ve tam enteral beslenmeye geçiş zamanları çalışma grubunda daha uzundu ve istatistiksel açıdan anlamlı idi. Çalışma grubundaki olgularda daha düşük doğum tartısı, daha fazla sayıda yaşa göre düşük ağırlıklı olgu sayısı, daha uzun süre total parental nutrisyon almaları, oral beslenmeye daha geç başlama ve tam enteral beslenme geçiş zamanının daha uzun olmasına rağmen taburculuktaki kiloları karşılaştırıldığında kontrol grubu ile aralarında istatistiksel açıdan anlamlı fark yoktu. Gruplar kilo artışı yönünden karşılaştırıldığında çalışma grubundaki bebeklerin daha fazla kilo aldığı gözlendi ve bu sonuç istatistiksel açıdan anlamlı idi. Çalışmamızda nekrotizan enterokolit açısından gruplar arasında istatistiksel açıdan anlamlı fark yoktu. Ancak çalışma grubundaki olgular evre 1'de kalırken, kontrol grubundaki olguların %33.3'nün evre 2' ye ilerlediği gözlendi.

Sonuç: Beslenme intoleransı olan prematüre bebeklerde B. laktis ve Hindiba inülini verilen grubun ağırlık artışının daha fazla oluşu ve neckrotizan enterokolitli olguların evrelerinin ilerlememesi probiyotik ve prebiyotiklerin olumlu etkileri olduğunu düşündürmektedir.

Anahtar kelimeler: Probiotikler, prebiotikler, beslenme intoleransı, prematüre bebekler.

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INTRODUCTION

Feeding intolerance occurs most commonly in very low birth weight (VLBW) infants, indicating a deficiency in the developmental pattern of gastrointestinal tract with decreasing gestational age (GA). Delay in enteral feeding causes decrease in enzyme levels, maturating intestinal motility and also atrophic changes start in intestinal mucosa[1,2]. In addition, delayed breastfeeding may also contribute to impairing or delaying acquisition of gut commensals such as bifidobacteria, resulting in an increased susceptibility to pathogenic colonization likely acquired from the neonatal intensive care unit (NICU)[3]. Ineffective digestion and prolonged passing time through the intestines due to immature digestion, absorption and motility may cause intestinal disturbances[4,5]. It is very important to tolerate the feeding for premature babies because of inadequate energy storage and high energy demand.

Despite the term's frequent usage in literature, a clear and universal definition of feeding intolerance is lacking. Feeding intolerance was often diagnosed using assessment findings including inability for enteral feeding, gastric residual, abdominal distention, guiac positivity, bradycardia, and desaturation attacks[6]. Most common findings of feeding intolerance are gastric residuals and abdominal distention. However, the majority of the researchers define feeding intolerance when the presence of gastric residual volume (GRV) is more than 1/2-1/3 of previous feeding[6-9].

Many different treatment modalities, including probiotics are experienced to overcome feeding intolerance and necrotizing enterocolitis (NEC). Several systematic reviews and meta-analyses of randomized trials evaluating the use of probiotics, prebiotics or synbiotics in preterm infants suggest a beneficial effect for the bacterial colonization of gut[3,10].

Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host by modulating the gut microbiota and interacting with innate and adaptive immunity[10]. The exact mechanisms of how probiotics improve the health of the hosts are not clear. The effects of probiotics tend to be specific to a particular strain, so that health benefit is not necessarily applicable to another strain[11,12]. Prebiotics are defined as nondigestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thereby improving host health[10]. Fructooligosaccarides, galactooligosaccarides and inulin are mostly used prebiotics. There are many reports supporting the positive effect of prebiotics on feeding tolerance and its safety[13-15].

When probiotics and prebiotics are administered simultaneously, the combination is termed synbiotics. The prebiotic in the synbiotic mixture improves the survival of the probiotic bacteria and stimulates the activity of the host's endogenous bacteria.

As the debate about the pros and cons of routine probiotic supplementation continues, many institutions are satisfied with the current evidence and wish to use probiotics routinely. Because of the lack of sufficient dosages and regimen results related to probiotics and prebiotics, clinician-friendly guidelines are urgently needed to optimize the use of probiotics and prebiotics in preterm neonates. The effects of these supplements on the growth of infants are still unknown.

In this study we evaluate the effect of Bifidobacterium lactis (as probiotic) and Hindiba Inulin (as prebiotic) on feeding intolerance of newborns and weight gain in neonatal intensive care unit.

MATERIAL AND METHODS

This is a prospective study of premature infants with feeding intolerance. Infants were admitted to tertiary NICU of Çukurova University, Faculty of Medicine between December 2010 and June 2013. Ninety eight premature infants with feeding intolerance who were smaller than 35 gestational weeks and lower than 2500 grams birth weight was taken in this study. Infants were randomized into two groups by balanced blocks using sealed envelopes when they were fed enterally but had feeding intolerance. First group was study group and consisted of 52 premature infants who had Bifidobacterium lactis + Hindiba inulin. Second group was the control group which consisted of 46 premature infants who had feeding intolerance but did not get pre-probiotics or prokinetic agent for this complaint. Infants with any

disease other than those linked to prematurity or congenital anomalies of the intestinal tract and whose parents refused to participate were excluded. Nine premature babies were withdrawn (five from study group and four from control group) due to death during the study. Deaths were due to respiratory reasons (two from control group, two from study group), cardiac reasons (one from control group, one from study group) and sepsis (two from control group, one from study group). Results were analyzed according to 89 premature babies.

Feeding intolerance was diagnosed with at least two of the following criteria: 1) Less than 75 ml/kg/day enteral feeding at the end of the first postnatal week, 2) Gastric residuals (gastric aspirate more than 50% of previous feeding volume), 3) Emesis/Vomiting, 4) Abdominal distention (increase in abdominal girth), 5) Gastrointestinal bleeding[6,8].

A database was kept routinely collecting all demographic, gestational and perinatal data including intrauterine growth retardation, gestational week, birth weight, gender, and Apgar scores at 1st and 5th minutes. Lubchenco growth chart was used to evaluate prenatal growth[16].

Factors related to mother; prolonged membrane rupture, preeclampsia, urinary tract infections and factors related to infants; respiratory distress syndrome, patent ductus arteriosus, need for inotropes and surfactant, umbilical catheterization, early onset sepsis, nosocomial infection, type and duration of nutrition, ventilatory support and antibiotic usage were recorded.

Total parenteral nutrition (TPN) starts at the first day of life with 2g/kg/day aminoacid and 1g/kg/day lipid infusions and these amounts are increased by 1 g/kg/day up to 3,5-4 g/kg/day for aminoacids and 3 g/kg/day for lipid solutions. Each sachet containing Bifidobactrium lactis, $5X10^9$ colony forming units, 30 mg plus *H* Inulin, 900 mg (Maflor, Mamsel Pharmaceutical Company, İstanbul, Turkey) were diluted with 10 mL distilled water and 1 mL of this dilution was given three times a day to the infants in the study group for ten days. Each sachet was used within 24 hours after dilution.

Duration of TPN, starting time of full enteral feeding(without IV nutrition) and starting time of oral feeding, daily weight gain were recorded. Type of nutrition was recorded as breast milk, formula, or breast milk + formula.

This trial was approved by the local ethics committee at the Çukurova University (Date: 30.06.2011, No:10/24). Infants were enrolled in the study after parental consent was obtained.

Statistical analysis

Statistical analyses were performed using the statistical package SPSS for Windows V.19.0 (Armonk, NY, IBM Corp, USA). Continuous variables are presented as the medians with minimum and maximum values, while categorical variables are given as frequencies and percentages. Differences for continuous variables the 2 groups were analyzed by Mann Whitney-U test whereas the $\chi 2$ test was used for categorical variables. In order to illustrate the descriptive statistics of continuous variables, and the differences between the two group's box plots were used. A p value of <0.05 was considered as statistically significant.

RESULTS

Demographics and clinical characteristics of the infants were given in Table 1. The gestational weeks of premature infants in both groups were similar; however the birth weight of the study group was lower. This difference was statistically significant ($p=0.02$). In addition 1st minute Apgar scores were lower in study group, whereas the 5th minute Apgar score was similar. In the study group, the mean starting day of Bifidobacterium lactis + Hindiba inulin was 9.9 ± 5.6 day. Procedures which were performed to the infants were given in Table 2. All procedures were similar in both groups.

When the nutritional characteristics of the two groups were evaluated, the mean duration of TPN was longer in study group with a statistical significance ($p=0.0001$) (Table 3). Starting time of full enteral feeding for the study group was longer than the control group (23.2 ± 7.1day and 15.4 ± 7.0 day respectively, $p=0.0001$) which was statistically significant. Oral feeding was started earlier in the control group and was statistically significant ($p=0.004$). The daily median weight gain in the study group infants was higher than the control group infants (17.2 g/day and 14.5 g/day respectively $p=0.038$).

Table 1. Demographics and clinical characteristics of the infants

	Study group n:47	Control group n:42	P
Gender			
Female (%)	20 (42.6)	20 (47.6)	0.395
Gestational week (wk) Median (Min-max)	31 (28-34)	31 (26-34)	0.901
Birth weight (g) Median (Min-max)	1270 (720-2140)	1410 (710-2500)	0.027
SGA (%)	16 (34.0)	9 (21.4)	0.139
AGA (%)	30 (63.8)	31 (68.5)	0.217
LGA (%)	1 (2.1)	2 (4.8)	0.457
Prolonged rupture of membranes (%)	5 (10.6)	6 (14.3)	0.420
Preeclampsia (%)	20 (42.6)	22 (52.4)	0.238
Apgar 1. min Median (Min-max)	5 (4-8)	6 (4-8)	0.041
Apgar 5. Min Median (Min-max)	8 (6-10)	8 (6-9)	0.130
Nozocomial infection (%)	17 (36.2)	11 (26.2)	0.217
Sepsis (%)	32 (68.1)	17 (40.5)	0.008
Positive blood culture (%)	17(37.0)	8 (24.2)	0.171
Necrotizing enterocolitis (%)	5 (10.6)	6 (14.3)	0.42
Stage 1 (%)	5 (100.0)	4 (66.7)	0.273
Stage 2 (%)	0 (0.0)	2 (33.3)	
Respiratory Distress Syndrome (%)	30 (63.8)	20 (47.6)	0.093
Patent Ductus Arteriosus (%)	1 (2.1)	2 (4.8)	0.475
Intraventricular hemorrhage (%)	3 (6.4)	3 (7.1)	0.606

SGA: small for gestational age, AGA: appropriate for gestational age, LGA: large for gestational age

Table 2. Clinical variables and interventions in two groups infants

	Study group n: 47	Control group n:42	P
Ventilator support (%)	41 (69.6)	34 (66.7)	0.475
Nasal CPAP (%)	33 (97.1)	28 (100.0)	0.548
Duration (hours) Median (Min-max)	37(5-408)	27.5 (12-155)	0.409
SIMV and SIPPV	9 (27,3)	10 (38.5)	0.263
Duration (hours) Median (Min-max)	48 (10-120)	48.5 (20-128)	0.967
Umbilical artery catheterization (%)	13 (27.7)	11 (26.2)	0.534
Umbilical artery duration (days) Median (Min-max)	6 (3-12)	7 (2-9)	0.726
Umbilical venous catheterization	25 (53.2)	21 (50.0)	0.465
Umbilical venous duration (days) Median (Min-max)	9 (1-14)	8 (3-15)	0.650
Inotropic usage (%)	7 (14.9)	3 (7.1)	0.208
Surfactant (%)	21 (44.7)	15 (35.7)	0.260
Antibiotic usage (%)	45 (95.7)	36 (85.7)	0.100

CPAP: Continous positive airway pressure, SIMV:Synchronized intermittent mandatory ventilation; SIPPV:Synchronized intermittent positive pressure ventilation

Table 3. Factors related to nutritional characteristics

	Study group n: 47	Control group n:42	P
Duration of TPN (days) Median (Min-max)	16(6-31)	11(2-35)	<0.0001
Type of enteral nutrition			
Breast milk (%)	8(17.0)	9(21.4)	0.397
Formula (%)	0(0.0)	1(2.4)	0.472
Breast milk + Formula (%)	39(83.0)	32(76.2)	0.297
Volume of first enteral feeding (mL/day) Median (Min-max)	12 (3-40)	16 (4-40)	0.197
Start time of full enteral feeding (days) Median (Min-max)	22 (9-38)	15 (4-38)	<0.0001
Start of oral feeding (days) Median (Min-max)	28(5-67)	14(2-64)	0.004

TPN: Total Parenteral Nutrition

Age of reaching the birth weight was similar between the groups. Although the duration of hospitalization was not statistically different, the mean weight at the day of discharge was similar (Table 4, Figure 1-2). The infants in control and study groups were subdivided according to birth weight as <1000 g, 1001-1500g and >1500g. Weight gain according to birth weights was analysed and given in Table 5. Weight gain was statistically significant in study group compared to control group in >1500 g birth weight (p=0.013)

Table 4. Weight status of the infants during hospitalization

	Study group n: 47	Control group n:42	P
Weight gain (g/day) Median(Min-max)	17.2 (8.0-38.7)	14.5 (6.4-50.1)	0.038
Day of reaching birth weight (days) Median (Min-max)	10 (6-25)	9 (4-29)	0.131
Age at discharge (days) Median (Min-max)	34 (13-75)	31 (16-82)	0.69
Weight at discharge (g) Median (Min-max)	1800 (1380-2280)	1830 (1560-2660)	0.285

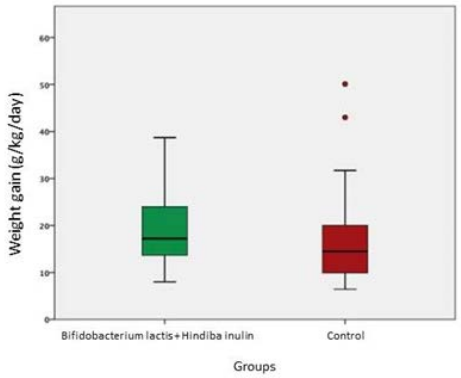

Figure 1. Weight gain of the infants (g/day)

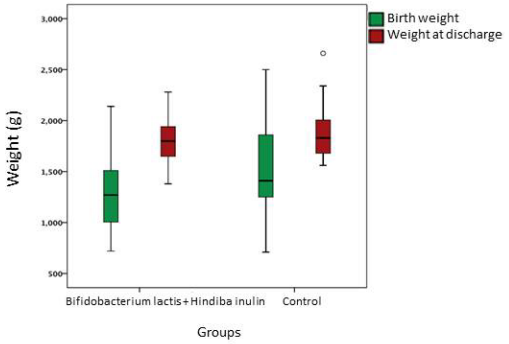

Figure 2. Birth weight and body weight at discharge of the infants.

Table 5. Weight gain accordingto birth weight of the infants

Birth weight	Weight Gain (g/day) Median (Min-Max)		p
	Study group n=47	Control group n=42	
<1000g	23 (10-36)	25 (15-32)	0.433
1001-1500g	15 (8-35)	15 (8-110)	0.769
>1500g	18 (10-33)	10 (6-93)	0.013

DISCUSSION

Preterm infants in NICU are at high risk of intestinal disturbances with proliferation of pathogenic microflora[3]. This is due to delayed introduction of enteral feeding, lack of fresh breast milk, frequent antibiotic use, and the neonatal intensive care unit environment[17]. By using prebiotics, probiotics and synbiotics, bacterial colonization of the intestines could be manipulated. Probiotic feeding of premature infants has emerged in the last years as a promising strategy to mimic the normal enteric gut composition of term breastfed infants. Thus, probiotics ensure preterm the wide range of benefits of commensal microflora may provide since birth[13,18]. ESPGAN reported that, there is insufficient evidence available suggesting the use of probiotics or prebiotics in preterm infants is safe[2]. In this study, we evaluate the effects of probiotic and prebiotic on feeding intolerance of newborns in our NICU. We used Bifidobacterium lactis as a probiotic and Hindiba inulin as a

prebiotic. Premature infants in both of the groups were followed for feeding intolerance.

Starting time of probiotics was reported as early as the first 4 hours of life till 7 days of life when the babies were ready for feeding. Duration of it was until corrected 35 gestational weeks or till discharge time (at least five days, 3-5x10^9-10^{11} CFU, single dose) in different studies[19,20]. Deshpande et al.[6] analyzed 11 studies about VLBW babies and reported that probiotics was started in first 10 days of life, while Dani et al.20 added probiotics after the first feeding till discharge of the babies, Lin et al.[2] used Lactobacillus acidophilus and Bifidobacterium infantis after the first week of life till discharge. We started Bifidobacterium lactis as probiotics at a mean postnatal 9.9 days and continued for 10 days in this study. Compared to the literature, we started probiotics later and the duration was shorter. This time difference might explain the lower positive effect of probiotics and prebiotics in feeding intolerance in contrast to the literature.

Monitoring weight gain evaluates the overall health of the infant and determines the adequacy of nutritional intake. Although the infants in the study group had lower birth weight, they gained more weight compared to the control group and this was statistically significant (17.2 g/day versus 14.5 g/day, p=0.038). With this more weight gain in the study group having prebiotic+probiotic, they have caught the weight of control group at discharge. There was no statistical difference between the two groups in terms of weight at discharge. Underwood et al.[22] studied different synbiotics and did not found significant differences between the groups for gains in weight. Mugambi et al.[23] reviewed and also reported that addition of synbiotics to infant nutrition did not have any significant effect on weight gain. Also Dilli et al.[24] reported that VLBW infants treated with the same synbiotic did not have significant weight gain compared to placebo or probiotics alone.

In recent years, several meta-analyses have been published that probiotics are beneficial to preterm infants by reducing the risk for NEC[25-30]. Consistent with this, necrotizing enterocolitis did not progress to higher grades in the study group compared to the control group in our study. Recently, Dilli et al.[24] reported that Bifidobacterium lactis alone or in combination with H. inulin reduces the incidence of NEC in VLBW infants. Öncel et al.[25] used Lactobacillus reuteri in their study and showed that there is no significant difference in terms of overall rate of NEC/death in their study group compared to control group.

In a Cochrane meta-analysis in 2014, Alfaleh et al.28 reported that probiotics administration did not decrease the total days of parenteral nutrition but had significant reduction in time to reach full enteral feeding. Premature infants in our study had TPN and continued according to the feeding tolerance. Duration of TPN was significantly longer in the study group (p=0.0001). Öncel et al.[25] also managed to demonstrate statistically significant reductions in TPN duration in their study.

Starting time of oral feeding and starting time of full enteral feeding were significantly longer in the study group compared to the control group (p=0.0001). This difference might be related to lower birth weight, lower Apgar scores and higher number of SGA infants in the study group.

Lin et al.[31] demonstrated the higher incidence of sepsis in babies with birth weight smaller than 750 g. Therefore, the use of probiotics is still controversial in babies with birth weight smaller than 1000 g [15,23,30]. Öncel et al.[25] showed that supplementation with L reuteri resulted in significant reductions in the frequency of proven sepsis and rates of feeding intolerance. In our study sepsis was significantly higher in the study group. Lower birth weight, lower Apgar scores and higher number of SGA infants might have played a role in the higher sepsis rates in the study group.

Our study has several limitations. First, the patients in the study group had lower birth weight and Apgar scores at the 1st minute, there were more babies with SGA in the study group. Second, the study was not powered to evaluate death in these groups. Third, we could not perform random stool testing to confirm the presence of colonization. The mean duration of probiotic and prebiotic supplementation was relatively short. These might influence the expected effects of probiotics or prebiotics.

Although there were more negative demographic data in the study group, gaining more weight than control group and catching the weight at discharge may strengthen the use of probiotics and prebiotics together in feeding intolerance especially in infants >1500 g birth weight. There was not enough evidence to state that synbiotics in infant formula have a significant effect on growth.

REFERENCES

1. Johnston M, Landers S, Noble L, Szucs K, Viehmann L. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129:827-41.
2. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. ESPGHAN Committee on Nutrition. Enteral nutrient supply for premature infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50:85-91.
3. Manzoni P, Lista G, Gallo E, Marangione P, Priolo C, Fontana P et.al. Routine Lactobacillus rhamnosus GG administration in VLBW infants: A retrospective, 6-year cohort study. Early Hum Dev 2011;81:35-8.
4. Di Lorenzo M, Bass J, Krantis A. An intraluminal model of necrotizing enterocolitis in the developing neonatal piglet. J Pediatr Surg. 1995;30:1138-42.
5. Lin J. Too much short chain fatty acids cause neonatal necrotizing enterocolitis. Med Hypotheses. 2004;62:291-93.
6. Moore TA, Wilson ME. Feeding intolerance; a concept analysis. Adv Neonatal Care. 2011;11:149-154.
7. Dodrill P. Feeding difficulties in premature infants. Infant Child Adolesc Nutr. 2011;3:324-31.
8. Alan S, Erdeve Ö. Enteral beslenmede gelişen sorunlar ve yönetimi. In: Prematüre Bebeğin Enteral Beslenmesi (Eds A Bülbül, HS Uslu, A Nuhoğlu):83-98. İstanbul, İstanbul Medikal, 2013.
9. Fanoro S. Strategies to improve feeding tolerance in premature infants. J Matern Fetal Neonatal Med. 2012;4:54-6.
10. Szajewska H. Probiotics and prebiotics in preterm infants: where are we? where are we going? Early Hum Dev. 2010;86;81-6.
11. Köksal N, Akpınar R, Köse HN, Sayrım K. Prematüre ve yenidoğan beslenmesi. Güncel Pediatri. 2003;1:59-72.
12. Weizman Z, Asli G, Alsheikh A. Effect of probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics. 2005;115:5-9.
13. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995;125:1401-12.
14. Brannon C. Prebiotics: feeding friendly bacteria. Today's Dietitian. 2003;14:123-8.
15. Lin PW, Nasr TR, Stoll BJ. Necrotizing enterocolitis: recent scientific advances in pathophysiology and prevention. Semin Perinatol. 2008;32:70-82.
16. Lubchenco LO, Hansman C, Boyd E: Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics. 1966;37:403-8.
17. Luoto R, Ruuskanen O, Waris M, Kalliomäki M, Salminen S, Isolauri E. Prebiotic and probiotic supplementation prevents rhinovirus infections in preterm infants: a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2014;133:405-13.
18. Fanaro S, Jelinek J, Stahl B, Boehm G, Kock R, Vigi V. Acidic oligosaccharides from pectin hydrolysate as new component for infant formulae: effect on intestinal flora, stool characteristics, and pH. J Pediatr Gastroenterol Nutr. 2005;41:186-90.
19. Deshpande GC, Rao SC, Keil AD, Patole SK. Evidence- based guidelines for use of probiotics in preterm neonates. BMC Med. 2012;9:92.
20. Dani C, Biadaioli R, Bertini G, Martelli E, Rubaltelli FF. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in premature infants: a prospective double-blind study. Biol Neonate. 2002;82:103-8.
21. Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics. 2005;115:1-4.
22. Underwood MA, Salzman NH, Bennett SH, Barman M, Mills DA, Marcobal A et al. A randomized placebo-controlled comparison of 2 prebiotic/probiotic combinations in preterm infants: impact on weight gain, intestinal microbiota, and fecal short-chain fatty acids. J Pediatr Gastroenterol Nutr. 2009;48:216-25.
23. Mugambi MN, Musekiwa A, Lombard M, Young T, Blaauw R. Synbiotics, probiotics or prebiotics in infant formula for full term infants: a systematic review. Nutr J. 2012;11:81.
24. Dilli D, Aydın B, Fettah ND, Özyazıcı E, Beken S, Zenciroğlu A et al. The propre-save study: effects of probiotics and prebiotics alone or combined on necrotizing enterocolitis in very low birth weight infants. J Pediatr. 2015;166:545-51.
25. Oncel MY, Sari FN, Arayici S, Guzoglu N, Erdeve O, Uras N et al. Lactobacillus Reuteri for the prevention of necrotising enterocolitis in very low birth weight infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2014;99:F110-5.
26. Guthmann F, Kluthe C, Buhrer C. Probiotics for prevention of necrotizing enterocolitis: an updated meta-analysis. Klin Pediatr. 2010;222:284-90.
27. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics. 2010;125:921-30.
28. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2014;4:CD005496.
29. Athalye-Jape G, Rao S, Patole S. Lactobacillus reuteri DSM 17938 as a probiotic for preterm neonates: a strain-specific systematic review. JPEN J Parenter Enteral Nutr. 2016;40:783-94.
30. Mihatsch WA, Braegger CP, Decsi T, Kolacek S,

Lanzinger H, Mayer B et al. Critical systematic review of the level of evidence for routine use of probiotics for reduction of mortality and prevention of necrotizing enterocolitis and sepsis in preterm infants. Clin Nutr. 2012;31:6-15.

31. Lin HC, Hsu CH, Chen HL. Oral probiotics prevent necrotizing enterocolitis in Very low birthweight premature infants: a multicenter, randomized, controlled trial. Pediatrics. 2008;122:693-700.