Slow verses rapid advancement of enteral feed in preterm neonates of 28-34 weeks of gestational age with abnormal antenatal umbilical artery Doppler: A randomised controlled trial

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Abstract

Background: Necrotising enterocolitis (NEC) is the commonest and most serious gastrointestinal neonatal emergency. In preterm infants with evidence of abnormal Doppler flow velocities in the fetal umbilical artery, suboptimal intestinal perfusion is postulated to increase the risk of feed intolerance and NEC.

Objectives: To compare the effect of slow versus rapid enteral feeding in preterm neonates with abnormal antenatal umbilical artery Doppler.

Method: This is a randomised controlled trial; we randomised into a slow and a fast group; we randomised separately into subcategories based on the weight. Sample size was calculated as 82. Data analysis was done using SPSS version 23. For group comparisons of categorical data, Chi-squared test was used. If expected frequency in the contingency tables was <5 for more than 25% cells, Fisher's exact test was used. For non-parametric continuous data Mann-Whitney test was applied. Statistical significance was kept at $p<0.05$ and power at 80%.

Results: In neonates with slow and rapid feeding with birth weight <1250g, percentage of 2b (30% and 26.7% respectively) was more compared to other stages, whereas in group with birth weight ≥1250g rapid feeding group Ia (14.3%) was more in slow feeding group and 1a and 2a equal in rapid feeding group with no statistical significance. The mean duration of stay hospital was less in rapid feeding group in both birth strata. The sepsis percentage was more in the slow feeding group. Regarding mortality in both groups, there was no statistical difference.

Conclusions: In this study the type of feeding did not affect NEC or feeding intolerance in preterm infants. Rapid feeding had a significant impact on sepsis and length of stay in preterm infants.

(Key words: Necrotising enterocolitis, Preterm, Hospital-stay, Sepsis)

Introduction

According to the World Health Organisation (WHO), a preterm birth is a live birth that occurs before 37 completed weeks of gestation[1]. The incidence of necrotising enterocolitis (NEC) varies from centre to centre and from year to year within centres. An estimated 0.3–2.4 cases occur in every 1,000 live births[2]. The incidence of NEC inversely correlates with gestational age at birth[2].

Umbilical Doppler flow abnormalities occur in 6% of high-risk pregnancies[3]. In preterm infants with evidence of abnormal Doppler flow velocities in the fetal umbilical artery, suboptimal intestinal perfusion is postulated to increase the risk of feed intolerance and NEC. A study by Bajwa NM, *et al*[4] found that the incidence of NEC was significantly higher in neonates with abnormal umbilical artery Doppler studies compared to those with normal studies (16.7% vs. 1.2%). Early introduction and advancement of enteral milk feeding may exacerbate the risk of NEC[4]. Although trial and observational data suggest that early initiation of enteral feeding is feasible, further studies are needed to determine whether slow versus rapid advancement of feed volumes affect important outcomes including feed intolerance, NEC, invasive infection, and cholestasis associated with prolonged administration of parenteral nutrition or intravenous fluids[5]. This issue is particularly pertinent to our clinical setting and most of the developing countries given the existing resource pressures (for example, limiting our capacity to provide parenteral nutrition) and the high level of risk factors associated with acquired invasive infection. Due to paucity of data as well as emphasizing the importance of early fading we started this study.

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Objectives

To compare the effect of slow versus rapid enteral feeding in preterm neonates with abnormal antenatal umbilical artery Doppler. The primary objective is to determine the incidence of feed intolerance and NEC in both groups. Secondary objectives include the incidence of sepsis in both groups at the time of discharge, duration of hospital stay in both groups and mortality in both groups.

Method

We included all eligible in-born neonates with absent end-diastolic flow (AEDF) who were ≥1000g and between 28 and 34 weeks of gestation within 6 hours after birth. Infants were weighed on an electronic weighing scale with 1 gram accuracy. Gestational age was assigned as per last menstrual period and first trimester ultrasound and confirmed postnatally by New Ballard's Score. We excluded infants with evidence of perinatal asphyxia (Apgar score at 5 minutes <6), shock or inotrope dependency, gastrointestinal tract or other major congenital malformation, or any other contraindication to the initiation of enteral feeds (Figure 1).

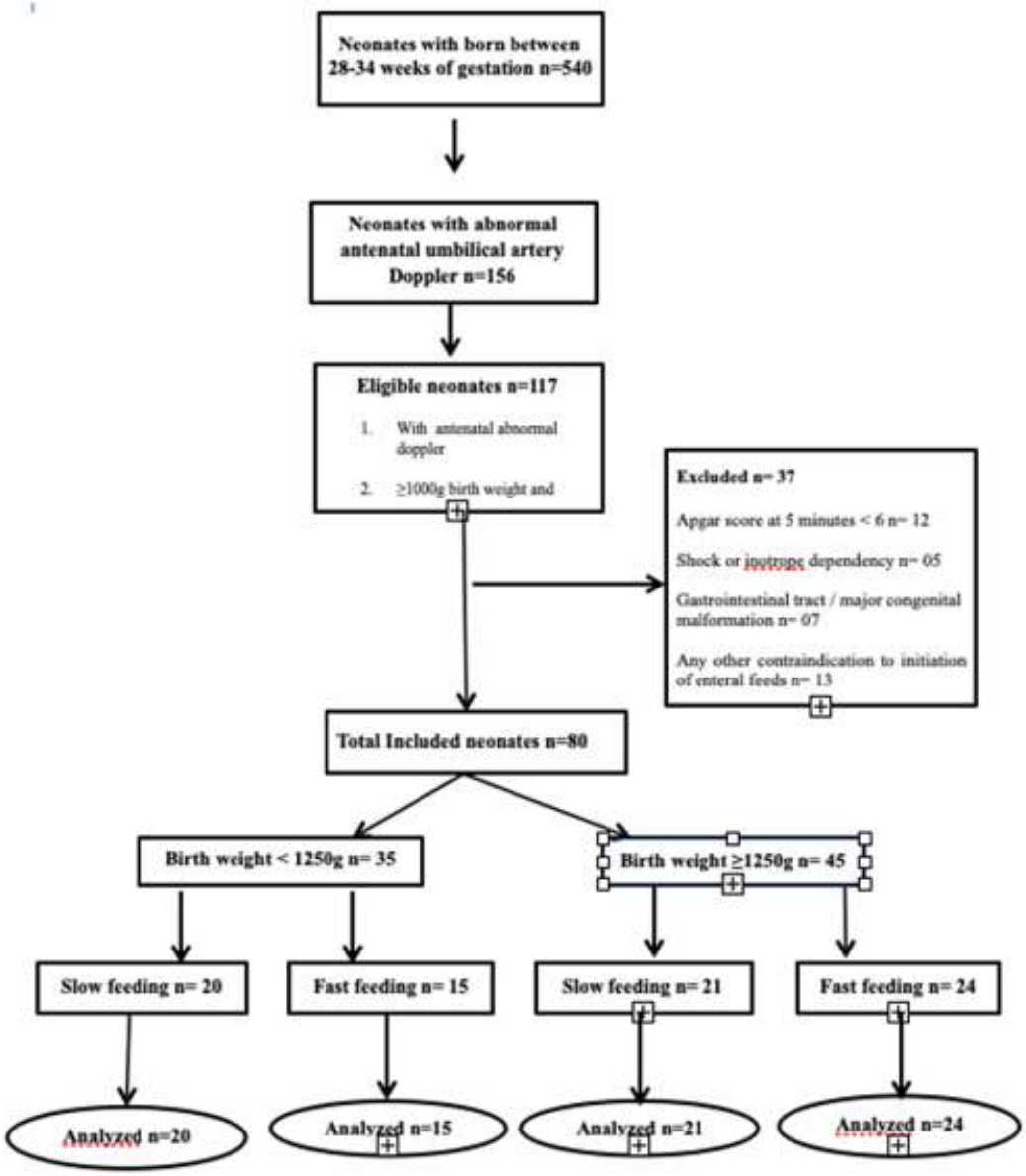

Figure 1: ***The flow of participants from enrolment till outcome***

The duration of the study was 24 months from May 2021 to May 2023. It was a randomized control trial.

Preterm neonates with abnormal antenatal doppler who were born in our hospital were included. The

sample size was calculated as 82 based on the formula $n = 2(Z + Z_\beta)^2 p(1-p)/(p_1 - p2)$ 2.. Reference parameters taken from the study[6]. We included 39 cases in the slow feeding group and 41 cases in the fast-feeding group due to the limitation of time in a thesis-research.

Eligible infants were randomly assigned between 6 and 72 hours postpartum using a computer-generated number assigned by an independent shield observer from an opaque envelope. An eligible neonate was randomly assigned to receive a slow or rapid stepwise increase in enteral feeding until a full intake of 150mL/kg/day was reached. In the group weighing less than 1250g, enteral nutrition was started at 10ml/kg/day and, from the second day of life, increased to 20 ml/kg/day in the slow group and 30 ml/kg/day in the rapid group. In contrast, in the 1250g group, enteral nutrition advanced to 30ml/kg/day and 40ml/kg/day in the slow and rapid groups, respectively, until full feeds.

If, after 6 hours, the abdomen was still not ready for feeding, the assessment was done and monitored for up to 72 hours. If feeds could not be initiated within 72 hours, they were excluded. EBM was preferred, but pasteurised donor human milk (PDHM) was used when unavailable. Key results were measured. In feed-intolerant infants, feed intake was withheld for 6 hours and reassessed after 6 hours. If the examination was normal, i.e., bowel sounds were present, there was no bloating, and there was no gastric aspiration, feeding was restarted at 10 mL/kg/day for infants weighing <1250g and 20 mL/kg/day for infants weighing 1250g, and feeding progressed as per proscribed plan. In the event of laboratory abnormalities or signs of feed intolerance that persisted or recurred, feeding was discontinued until full recovery and then resumed as scheduled.

Ethical issues: Approval for the study was obtained from the Institutional Ethics Committee of Osmania Medical College, Hyderabad, India (No. ECR/300/Inst/AP/2013/RR-30). The study was registered under the Clinical Trials Registry of India (Reference number REF/2021/ 06/069048**).** Written informed consent was obtained from the parents of the neonates

Statistical analysis: The MS Excel spreadsheet programme was used to code and record data collected from ICU patients. Data analysis was done by using SPSS version 23 (IBM Corp.). Descriptive statistics were used to summarise the data. For group comparisons of categorical data, Chi-squared test was used. If the expected frequency in the contingency tables was less than 5 for more than 25% of the cells, Fisher's Exact test was used. For non-parametric continuous data, Mann-Whitney test was applied. Statistical significance was kept at $p<0.05$ and power at 80%.

Results

Table 1 shows the baseline characteristics in slow versus rapid feeding groups with respect to birth weight categories.

Table 1: ***Baseline characteristics in slow versus rapid feeding groups with respect to birth weight categories***

Variable	Group-1 <1250g (n=35)		p-value	Group- 2 ≥1250g (n=45)		p-value
	Slow (n=20)	Rapid (n=15)		Slow (n=21)	Rapid (n=24)	
Birth weight (g) Mean ± SD	1192.5 ±154.17	1175.33 ± 61.86	**0.006***	1476.9 ±144.45	1427.08 ± 59.09	**0.002***
Gestational age (weeks) Mean± SD	30.30 ± 1.22	29.87 ± 0.35	**0.00***	33 ± 1.52	32.71 ± 0.81	0.07*
Gender n (%)						
Female	13 (65)	05 (66.7)	0.06**	10 (47.6)	13 (54.2)	0.66**
Male	07 (35)	10 (33.3)		11 (52.4)	11 (45.8)	
Mother's age Mean ± SD	26.20 ± 2.48	25.47 ± 3.11	0.44*	27.95 ± 2.87	25.17 ± 2.33	0.09*
Mode of conception n (%)						
Spontaneous	17 (85)	13 (86.7)	1.00#	21 (100)	19 (79.2)	0.05#
In vitro fertilisation	03 (15)	02 (13.3)		0 (0)	05 (20.8)	
Mode of delivery n (%)						
Normal vaginal delivery	19 (95)	14 (93.3)	1.00#	18 (85.7)	12 (50)	**0.01****
Lower segment caesarean section	01 (5)	01 (6.7)		03 (14.3)	12 (50)	
Co-morbidities n (%)						
Pregnancy induced hypertension	20 (100)	14 (93.3)	0.43#	20 (95.2)	24 (100)	0.47#
Gestational diabetes mellitus	03 (15)	02 (13.3)	1.00#	0 (0)	08 (33.3)	**0.004**#
PROM/Chorioamnionitis n (%)						
Present	18 (90)	13 (86.7)	1.00#	08 (38.1)	14 (58.3)	0.18**
Absent	02 (10)	02 (13.3)		13 (61.9)	10 (41.7)	
Antenatal steroids given. n (%)						
Yes	16 (80)	12 (80)	1.00#	18 (85.7)	23 (95.8)	0.33#
No	04 (20)	03 (20)		03 (14.3)	01 (4.2)	

**Unpaired t-test, **Chi-square test, # Fischer exact test PROM: Prolonged rupture of membranes*

Among 80 eligible neonates, 35 (43.8%) were of birth weight <1250g and 45 (56.2%) were of birth weight ≥1250g; 39 were in the rapid feeding group and 41 were in the slow feeding group. Comparatively, birth weight was more in the slow-feeding group than the rapid-feeding group and this

was statistically significant in both weight categories. The frequency of NEC was more in the group with birth weights less than 1250g (55% and 53.3%) compared to neonates with birth weights more than 1250g (23.8 and 16.7). However, the difference was not statistically significant (p= 0.55). Table 2 shows the distribution of stages of NEC in slow versus rapid feeding groups with respect to birth weight categories.

Table 2: ***Distribution of stages of necrotizing enterocolitis (NEC) in slow versus rapid feeding groups with respect to birth weight categories***

NEC stage	Group 1 <1250g (n=35)		p-value*	Group 2 ≥1250g (n=45)		p-value*
	Slow (n=20)	Rapid (n=15)		Slow (n=21	Rapid (n=24)	
No	09 (45)	07 (46.7)	0.84	16 (76.2)	20 (83.3)	0.86
1a	04 (20)	02 (13.3)		03 (14.3)	02 (8.3)	
1b	0 (0)	0 (0)		0 (0)	0 (0)	
2a	01 (5)	02 (13.3)		02 (9.5)	02 (8.3)	
2b	06 (30)	04 (26.7)		0 (0)	0 (0)	
3a	0 (0)	0 (0)		0 (0)	0 (0)	
3b	0 (0)	0 (0)		0 (0)	0 (0)	

**Fischer exact test*

Among neonates with slow and rapid feeding with birth weight <1250g group, the percentage of 2b (30% and 26.7 respectively) was more compared to other stages whereas in the group with birth weight ≥1250g rapid feeding group 1a (14.3) was more in the slow feeding group and 1a and 2a equal in the rapid feeding group with no statistical significance.

Table 3 shows the distribution of feed intolerance among slow versus rapid feeding groups with respect to birth weight categories.

Table 3: ***Distribution of feed intolerance among slow versus rapid feeding groups with respect to birth weight categories***

Feed intolerance	Group 1 <1250g (n=35)		p-value*	Group 2 ≥1250g (n=45)		p-value*
	Slow (n=20)	Rapid (n=15)		Slow (n=21)	Rapid (n=24)	
Yes	11 (55)	08 (53.3)	0.92	06 (28.6)	04 (16.7)	0.34
No	09 (45)	07 (46.7)		15 (71.4)	20 (83.3)	

**Chi-square test*

The percentage of feed intolerance was more in both rapid and slow feeding groups in group 1 with birth weight <1250g compared to group 2. However, the difference was not statistically significant.

Table 4 shows the distribution of sepsis at discharge among slow versus rapid feeding groups with respect to birth weight categories.

Table 4: ***Distribution of sepsis at discharge among slow versus rapid feeding groups with respect to birth weight categories***

Sepsis at discharge	Group 1 <1250g (n=35)		p-value*	Group 2 ≥1250g (n=45)		p-value*
	Slow (n=20)	Rapid (n=15)		Slow (n=21)	Rapid (n=24)	
Present	17 (85)	07 (46.7)	**0.04***	12 (57.1)	06 (25)	**0.03**[#]
Absent	03 (15)	08 (53.3)		09 (42.9)	18 (75)	

**Chi-square test, # Fischer exact test*

Among 80 neonates, sepsis percentage was more in the slow feeding group than in the rapid feeding group (85% vs 46.7 and 57.1 vs 25% respectively in groups 1 and 2) and this was statistically significant indicating a relationship between the type of feeding and sepsis.

Table 5 shows the distribution of mortality among slow versus rapid feeding groups with respect to birth weight categories.

Table 5: ***Distribution of mortality in slow versus rapid feeding groups with respect to birth weight categories***

Mortality	Group 1 <1250g (n=35)		p-value*	Group 2 ≥1250g (n=45)		p-value*
	Slow (n=20)	Rapid (n=15)		Slow (n=21)	Rapid (n=24)	
Discharge	14 (70)	09 (60)	0.72*	16 (76.2)	22 (91.7)	0.23[#]
Death	06 (30)	06 (40)		05 (23.8)	02 (8.3)	

**Chi-square test, # Fischer exact test*

The percentage of mortality was more in group 1 (30 and 40) compared to group 2 (23.8 and 8.3) but this was not statistically significant.

Table 6 shows the mean duration of hospital stay among slow versus rapid feeding groups with respect to birth weight categories.

Table 6: ***Mean duration of hospital stay among slow versus rapid feeding groups with respect to birth weight categories***

Duration of hospital stay(days)	**Group 1 <1250g (n=35)**		**p-value***	**Group 2 ≥1250g (n=45)**		**p-value***
	Slow (n=20)	**Rapid (n=15)**		**Slow (n=21)**	**Rapid (n=24)**	
Mean ± SD	28.05 ± 8.2	23.67 ± 6.16	**0.01**	21.95 ± 7.26	19.13 ± 5.81	**0.04**

**Unpaired t- test*

The mean duration of stay in the hospital was less in the rapid feeding group in both birth strata compared to the slow feeding group with a statistically significant difference. more in group 2 (21 Vs 19) than in group 1 (28 Vs 23). Signs of thrombocytopenia, blood in stools, abdominal tenderness, C-reactive protein and blood culture were all more in group <1250g compared to group ≥1250g with an increase in slow-feeding neonates than rapid-feeding neonates.

Discussion

The purpose of this randomised control trial was to compare the effect of slow versus rapid enteral feeding in preterm neonates with abnormal antenatal umbilical artery Doppler. The likelihood of complications is higher for preterm neonates who have abnormal antenatal Doppler of the umbilical artery, such as absent or reverse end diastolic flow (AREDF), increased resistance to blood flow in the ductus venous and inferior vena cava, or middle cerebral artery redistribution[7]. The baseline characteristics were similar in both groups and no statistical difference was found except for gestational age in groups less than 1250g and concerning birth weight in both groups. The overall percentage of abnormal umbilical artery abnormality was almost the same in both males and females and showed no gender-wise difference similar to the finding in the study by Jain S, *et al*[6]. Type of conception, co-morbidities in mothers and administration of antenatal steroids showed no significant difference among slow and rapid feeding group with respect to birth strata.

The elevated incidence of NEC in newborns with prenatal Doppler abnormalities has been demonstrated, with odds of 2.13 and 95% confidence interval of 1.4-3.0 compared to controls without AREDF, according to a comprehensive evaluation of 14 observational research investigations[8]. In our current study, overall incidence of NEC among all preterm newborns was 35%, but it was 39% and 31% in the slow and rapid feeding groups, respectively. These numbers are similar to those found in a study by Leaf A, *et al*[8] (39% and 38%). Contrary to our study finding, Jain S, *et al*[6] showed relatively low incidence (10% and 7.5%).

No statistical difference was found in the incidence of NEC concerning staging among both groups. Despite beginning early and progressing feeds quickly in a chosen stable group of AEDF newborns, Jain S, *et al*[6] found a similar incidence of NEC overall and at any stage to that of the ADEPT trial. Concerning birth weight, neonates with >1250g had lesser incidence of NEC in both slow and rapid feeding neonates (23.8% and 16.7%) compared to neonates with <1250g slow and rapid feeding neonates (55% and 53.3%) but this was not statistically significant indicating that birth weight did not have an impact with the incidence of NEC contrary to the study by Karagianni P, *et al*[9]. Rapid feeding was not associated with more NEC than delayed feeding in our study, similar to a systemic review and metanalysis[10],

The overall incidence of feed intolerance was 36% in our trial. We did not detect any significant difference between the groups whereas it was 28% in a study by Jain S, *et al*[6] and 45% in a study by Aaradhya AS, *et al*[11]. These findings are by those reported in the Cochrane review[12].

The mean duration of hospital stay was decreased by rapid feeding (23 and 19 in groups with birth weight less than 1250g and ≥ 1250g respectively) in both birth weight groups compared to slow feeding groups (28 and 21 in groups with birth weight less than 1250g and ≥1250g respectively) and was statistically significant indicating rapid feeding would decrease the duration of hospital stay. In another investigation, Krishnamurthy S, *et al*[13] employed 30 ml/kg/day feed in the rapid feeding group and reported that the average duration of stay was lower than in the slow feeding group (median 9.5 days vs. 11 days) (p=0.003). These infants additionally gained weight back after birth more quickly. Similar findings were made by Salhotra A, *et al*[14] and Caple J, *et al*[15]. They reported that newborns in the rapid advancement group stayed less time in the hospital (10 ±1.8 days) as well as acquired body weight more quickly (median 18 days) compared to infants in the slow feeding group.

Similar results with shorter hospital stays were seen in a study by Fayyaz M, *et al*[16] who used quick feeding. Because anomalous prenatal umbilical artery anomalies were not taken into account in these investigations, it is important to be cautious when interpreting the results of these studies.

The overall percentage of sepsis is less in the rapid feeding group compared with the slow feeding group irrespective of the birth weight (33% vs 71%) which can be explained by decreased duration of hospital stay and decreased exposure to infections in the hospital in the rapid feeding groups. Similar findings were seen in the studies by Jain S, *et al*[6] and in a Cochrane review[17] showing decreased sepsis rate in rapid feeding groups compared with slow feeding group.

The mortality rates were 27% and 21% among slow and rapid feeding groups respectively suggesting no association between the type of feeding and mortality rate. Birth weight <1250g and ≥1250g did not find any association with mortality in our study similar to the findings of the study by Jain S, *et al*[6]. Contrary to our finding study by Karagol BS, *et al*[18] showed very low mortality rates of 9% and 7% among both groups which might be due to difference in inclusion criteria for birth weight and amount of advancement of milk.

Some variables in randomisation were statistically significant and this is one of the limitations of the study**.** The lack of power of the study due to the small sample size raises questions about the generalizability of the data. The lack of double blinding (masking the investigators to the assigned intervention) could have caused bias. Failure to consider additional considerations, such as regaining birth weight, hypotension, ventilation, etc. are also limitations of the study.

Conclusions

The findings of this randomised study suggest that the type of feeding may not significantly affect the incidence of NEC or feeding intolerance in preterm infants with low birth weight, gestational age 28-32 weeks and abnormal antenatal Doppler finding. Furthermore, regardless of birth weight, rapid feeding had a substantial impact on sepsis and the length of the inpatient trial.

References

1. Born too soon: The global action report on preterm birth [cited 2023 May 23]. Available from: https://www.who.int/publications-detail-redirect/9789241503433

2. Ginglen JG, Butki N. Necrotizing enterocolitis. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513357/

3. Barone G, Maggio L, Saracino A, Perri A, Ramagnoli C, Zecca E. How to feed small for gestational age newborns. *Italian Journal of Pediatrics* 2013; **39**: Article No.28. https://doi.org/10.1186/1824-7288-39-28 PMid: 23663313 PMCid: PMC3660241

4. Bajwa NM, Berner M, Worley S, Pfister RE, Zeilinger G, Bührer C, *et al.* Population-based age stratified morbidities of premature infants in Switzerland. *Swiss Medical Weekly* 2011; **141**: 1–6. https://doi.org/10.4414/smw.2011.13212 PMid: 21706450

5. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, *et al.* National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012; **379**(9832): 2162–72. https://doi.org/10.1016/S01406736(12)60820-4 PMid: 22682464

6. Jain S, Mukhopadhyay K, Jain V, Kumar P. Slow versus rapid enteral feed in preterm neonates with antenatal absent end diastolic flow. *Journal of Maternal-Fetal and Neonatal Medicine* 2016; **29**(17): 2828–33. https://doi.org/10.3109/14767058.2015.1105954 PMid: 26452650

7. Dorling J, Kempley S, Leaf A. Feeding growth restricted preterm infants with abnormal antenatal Doppler results. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2005; **90**(5): F359-63. https://doi.org/10.1136/adc.2004.060350 PMid: 16113150 PMCid: PMC1721930

8. Leaf A, Dorling J, Kempley S, McCormick K, Mannix P, Linsell L, *et al.* Abnormal Doppler Enteral Prescription Trial Collaborative Group. Early or delayed enteral feeding for preterm growth-

restricted infants: a randomized trial. *Pediatrics* 2012; **129**(5): e1260-8. https://doi.org/10.1542/peds.2011-2379 PMid: 22492770

9. Karagianni P, Briana DD, Mitsiakos G, Elias A, Theodoridis T, Chatziioannidis E, *et al.* Early versus delayed minimal enteral feeding and risk for necrotizing enterocolitis in preterm growth-restricted infants with abnormal antenatal Doppler results. *American Journal of Perinatology* 2010; **27**(5): 367-73. https://doi.org/10.1055/s-0029-1243310 PMid: 20013579

10. Anne RP, Aradhya AS, Murki S. Feeding in preterm neonates with antenatal Doppler abnormalities: A Systematic Review and Meta-Analysis. *Journal of Pediatric Gastroenterology and Nutrition* 2022; **75**(2): 202–9. https://doi.org/10.1097/MPG.0000000000003487 PMid: 35653426

11. Aradhya AS, Mukhopadhyay K, Saini SS, Sundaram V, Dutta S, Kumar P. Feed intolerance in preterm neonates with antenatal reverse end diastolic flow (REDF) in umbilical artery: a retrospective cohort study. *Journal of Maternal-Fetal and Neonatal Medicine* 2020; **33**(11): 1846–52. https://doi.org/10.1080/14767058.2018.1531123 PMid: 30373425

12. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database Systematic Reviews* 2017; **8**(8): CD001241. https://doi.org/10.1002/14651858.CD001241.pub7 PMid: 28854319 PMCid: PMC6483766

13. Krishnamurthy S, Gupta P, Debnath S, Gomber S. Slow versus rapid enteral feeding advancement in preterm newborn infants 1000-1499 g: a randomized controlled trial. *Acta Paediatrica* 2010; **99**(1): 42–6. https://doi.org/10.1111/j.16512227.2009.01519.x PMid: 20002013

14. Salhotra A, Ramji S. Slow versus fast enteral feed advancement in very low birth weight infants: a randomized control trial. *Indian Pediatrics* 2004; **41**(5): 435–41.

15. Caple J, Armentrout D, Huseby V, Halbardier B, Garcia J, Sparks JW, *et al*. Randomized, controlled trial of slow versus rapid feeding volume advancement in preterm infants. *Pediatrics* 2004; **114**(6): 1597–600. https://doi.org/10.1542/peds.2004-1232 PMid: 15574620

16. Fayyaz M, Haider S, Khan AH, Nazir S, Hassan A, Hussain SM. Comparison of slow versus rapid feeding regimen in preterm neonates in the reduction of hospital stay. *Journal of Rawalpindi Medical College* 2020; **24**(3). https://doi.org/10.37939/jrmc.v24i3.1384

17. Samuels N, van de Graaf RA, de Jonge RCJ, Reiss IKM, Vermeulen MJ. Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies. *BMC Pediatrics* 2017; **17**(1):105. https://doi.org/10.1186/s12887-017-0847-3 PMid: 28410573 PMCid: PMC5391569

18. Karagol BS, Zenciroglu A, Okumus N, Polin RA. Randomized controlled trial of slow vs rapid enteral feeding advancements on the clinical outcomes of preterm infants with birth weight 750-1250 g. *Journal of Parenteral and Enteral Nutrition* 2013; **37**(2): 223–8. https://doi.org/10.1177/0148607112449482 PMid: 22664861