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RESEARCH ARTICLE

RESPIRATORY DISTRESS SYNDROME OF PREMATURITY AND TIME TO REACH FULL FEEDS IN SMALL FOR GESTATIONAL AGE AND APPROPRIATE FOR GESTATIONAL AGE PRETERM NEONATES IN LESS THAN 34 WEEKS OF GESTATION

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Abstract

Background :Prematurity is a significant public health problem around the world because of the mortality and the associated short term and long-term morbidities.In the perinatal period of premature infants, especially very preterm (28- 32 weeks gestation) and extreme preterm (less than 28 weeks gestation) neonates are noticed to have respiratory distress syndrome of prematurity and its related complications and hence often considered to be too unstable to be fed enterally. Very immature and sick infants are started with total parenteral nutrition (TPN) which results in greater periods of enteral fasting.This study aims to assesses the effect of respiratory distress syndrome on feed intolerance by assessing time to reach full feeds in SGA and AGA preterm (less than 34 weeks gestation) neonates, while on a standardized institutional feeding protocol for preterm infants. It also aims to establish the time to reaching full feeds, in preterm AGA and SGA neonates.

Objective:To asses effect of respiratory distress syndrome of prematuri ty on time to reach full feeds in preterm Appropriate for gestational age (AGA) and Small for gestational age (SGA) neonates less 34 weeks of gestation.

Methods :This is a hospital based prospective cohort studyconducted at a 59-bedded tertiary level neonatal referral centre at a Medical College and teaching hospital on Preterm neonates of less than 34 weeks of gestation in the duration of September 2018 to June 2020.

Results :In our study, of the total enrolled neonates (n=160), 60.6% (n=97) were AGA neonates, while 39.4% % (n=63) were SGA neonate s. The median gestational age in the AGA cohort is 30 weeks (Range: 26- 33 weeks), and that in SGA cohort is 32 weeks (Range: 28- 33), with median birth weight of 1260 grams (800-2000g) and 1160 grams (750-1600g) in the AGA and SGA groups respectively. Male neonates constituted 48.12% of the entire cohort (n=77).

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In this study, the univariate analysissuggests factorsignificantly affecting TFF in AGA and SGA neonates was administration of surfactant and caffeine (indicating severity of respiratory disease). In the multivariate analysis howeverthe factors significantly impacting the TFF in SGA and AGA group were surfactant administration and mechanical ventilation >96 hours, caffeine.Incidence of RDS overall did not significantly affect time to reach full feeds in either of the two groups.
Conclusion: In this study, factors significantly impacting the time to reach full enteral feeds in SGA and AGA group were administration of surfactant, caffeine and mechanical ventilation for >96 hours. This study establishes that interventions done for RDS caused feed intolerance.

Introduction:-

Prematurity is a significant public health problem around the world because of the mortality and the associated short term and long-term morbidities. It is also the leading cause of neonatal deaths.In India, out of 27 million babies born each year, 3.5 million babies are born preterm giving it one of the highest incidences of preterm births globally.The largest burden of Small for gestational age (SGA) neonates has been recorded in South Asia where prevalence and neonatal mortality related to SGA is 34% and 26%, respectively(1).While SGA babies could be constitutionally small, a larger proportion of the SGA babies are due to fetal or intrauterine growth restriction due to various causes like maternal nutritional deficiencies, infections during pregnancy, abnormal placental function or fetal malformations. Therefore, Infants born both premature and small for gestational age carry a considerably higher risk of mortality and morbidity in the neonatal period and beyond.(2)

Premature infants require admission into Neonatal Intensive Care Units (NICU) due to organ immaturity and acute perinatal complications such as Respiratory Distress Syndrome (RDS), Bronchopulmonary Dysplasia (BPD), Hypoglycemia, Hypothermia, Hyperbilirubinemia, Feeding difficulties etc. Each of these perinatal complications impacts hospital stay and NICU course of the neonate. Premature infants are also more prone to infections and sepsis, because of their poor immuno-protective mucosal barriers and immature immune response. All the above-mentioned disease processes, the medical interventions and medications in the perinatal period, such as therapeutic use of caffeine citrate, inotropes, antibiotics, transfusion of blood products and mechanical ventilation also affects the intestinal hormonal dynamics, gastric emptying time, splanchnic perfusion, and gut friendly microbiota. SGA neonates often have placental insufficiency in the antenatal period, which results in redistribution of blood flow, impaired gut function, and intolerance to feeds, as well as increased incidence of NEC.(3) Premature infants, especially very preterm (28- 32 weeks gestation) and extreme preterm (less than 28 weeks gestation) neonates are noticed to have multiple complications, and hence often considered to be too unstable to be fed enterallywhich results in greater periods of enteral fasting. Such enteral fasting contributes to intestinal mucosal atrophy, intestinal barrier dysfunction, decreased digestive and absorptive capacity, increased colonization with pathogenic bacteria, and cholestasis(4). Enteral fasting not only affects time to reach Full Enteral Feed (FEF), and therefore growth of the infant, but also affects duration of stay in NICU, and may delay discharge.

About 80% infants born <27 weeks gestation will develop respiratory distress syndrome (RDS). Although respiratory distress is less common in infants born at 33- 36 weeks of gestation and is rare in full-term infants, it can be severe, with a 5% mortality rate.(5)By approximately 30-32 weeks gestation, the lungs make surfactant, which helps keep the alveoli open by reducing surface tension in the alveoli. Surfactant is a complex mixture of phospholipids, neutral lipids and surfactant specific proteins, and is synthesized, and secreted by type 2 pneumocytes in the alveoli. Infants born before 28-30 weeks gestation lack mature alveolar cells. RDS results from absent or insufficient surfactant due to developmental immaturity of type 2 pneumocytes, spontaneous or inherited mutations of surfactant related genes, or inactivation of surfactant due to inflammation, chemical modification or lung injury. Soon after birth, preterm infants with RDS develop rapid breathing, grunting, poor colour, and crackling or diminished breath sounds breathing requires increased work. Respiratory failure because of fatigue, apnoea, hypoxia, or an air leak (from alveolar injury) results from stiff lungs that need high pressures for ventilation(6).
RDS is an acute illness treated with respiratory support (oxygen, positive airway pressure, ventilator, or surfactant) as needed and improves in 2 to 4 days and resolves in 7 to 14 days. The aim of the management of RDS is to provide interventions that maximize survival whilst minimizing potential adverse effects.(5)It has been established that delayed gastric emptying and impairment of intestinal peristalsis occur in critically ill ventilated neonates. The mechanisms involved in delayed gastric emptying in patients with respiratory insufficiency can be explained as severe hypoxemia is associated with a transitory delay in gastric emptying. The inhibitory effect of somatostatin on gastrointestinal motility is another possible explanation for the delayed gastric emptying. Somatostatin is elevated in very low birth weight infants with pulmonary diseases requiring respiratory assistance.(6)

Caffeine citrate acts by antagonism of adenosine, a neurotransmitter that can cause respiratory depression by blocking both its inhibitory A1 and excitatory A2A receptors increases carbon dioxide sensitivity and decreases periodic breathing and decreases hypoxic depression of breathing(7).A potential association between the administration of caffeine and the development of medical or surgical necrotizing enterocolitis in premature infants exists.(8)It has also been established that use of caffeine results in delayed gastric emptyingand poor weight gain. This finding was attributed to the increased metabolic rate and increased oxygen consumption caused by the drug.(9) This study aims to study effect of RDS on feed intolerance by assessing time to reach full feeds in SGA and AGA preterm (less than 34 weeks gestation) neonates, while on a standardized institutional feeding protocol for preterm infants. Therefore, this study will help in identification of the risk factors affecting time to reach full feeds in preterm neonates less than 34 weeks, and thereby will aid in early prevention strategies to reduce the length of NICU stay and promote better outcomes.

Methodology:-

This is a hospital based prospective cohort studyconducted at a 59-bedded tertiary level neonatal referral centre at a Medical College and teaching hospital in the duration of March 2022 to August 2022 on Preterm neonates of less than 34 weeks of gestation Preterm neonates less than 34 weeks of gestation admitted in NICU were included in 2 cohorts 1. Appropriate for gestational age (Birth weight between 10^{th} to 90^{th} centile on intergrowth 21 charts) 2. Small for gestational age (Birth weight less than 10^{th} centile on intergrowth 21 charts). Neonates with Congenital anomalies of cardiopulmonary, neurological, craniofacial and gastrointestinal in origin and requiring surgical intervention within first 7 days of life which were likely to impact progress to enteral feeds and neonates who died before progress to full enteral feeds were excluded from the study.The institutional ethics committee approval and written informed consent of parents of eligible babies was obtainedbefore commencing the study. The antenatal, neonatal demographic and outcome data were collected. The following data which included likely risk factors to progress to full feed were collected: gestational age, anthropometry (birth weight, length and head circumference), sex, mode of delivery, occurrence of respiratory distress syndrome (RDS) ,use of inotropic drugs, caffeine.An Institutional standardized feeding protocol was adopted**.**Full Enteral feeds (FEF) was defined as 160 mL/kg per day of fortified human milk/ human milk/ pasteurized donor human milk/ mixed feed (Expressed breast milk and donor milk or formula milk) and if all else not available, formula feed.

Feeding tolerance was determined as acomposite of the following clinical symptoms:

1. Recurrent Vomiting
2. Abdominal examination – Distension or tenderness on palpation, girth measurement was performed in case of distension, and increase in girth more than 2 cm above baseline was considered significant.
3. Gastric residual Volumes − Changes in quantity of fluid (increased volumes) or change in colour to dark green (bilious) or red (blood)

Any of these symptoms which warranted the clinician to withhold feeds for a period of 12 hr or more was considered to have ‘Feed Intolerance’

Study design chart:-

Preterm neonates less than 34 weeks of gestation admitted to NICU identified from NICU admission book.

Counselling and study explained to mother

Consent and enrolment into the study
Demographic details, antenatal, intra-natal and postnatal history was noted on approved pre designed case record proforma
Anthropometrical parameters like Weight, Length, Head Circumference noted at the time of admission and discharge.

Information on time of initiation of enteral feeds, and grading up of feed, followed up every- day till the neonate reached full enteral feeds (FEF). All neonates were started on standard feeding regimen according to institutional guidelines.

RDS, need for Mechanical ventilation and Surfactant Therapy, medical interventions like Inotropes, caffeine, and blood transfusions noted.

Data entered into excel sheet and analysis done

Statistical tools:-

The data collected was coded and entered in Microsoft excel 2013. The continuous data were calculated in the form of mean; while the discrete data were calculated in the form of number and percentage or median values. The Shapiro Wilk test was used to analyse the spread of the data and it was not found to be normally distributed. Hence all non- parametric tests relevant to the data type and study parameters were employed.

The Chi square test was used for comparison of discrete data. Median values were compared using the Wilcoxon rank sum test (since the data was not normally distributed). Univariate and Multivariate analysis were done to compare the effect on the time required to reach the full feed of different parameters. Mann Whitney U test was used for the comparison of the median values between the two divisions (AGA and SGA) with respect to 4 different parameters.
All the p- values less than 0.05 were considered to be statistically significant.
Statistical package for Social Software (SPSS) 22.0; IBM Analytics, New York, U.S.A was used for carrying out the analysis. The data is presented in graphical and tabular format.

Results:-

Table 1. Perinatal Characteristics and clinical features of the cohort of SGA and AGA neonates

	Total (n=160)	SGA(n=63)	AGA(n=97)	P value
PERINATAL CHARACTERISTICS				
GA (weeks), median(range)	32 (26- 33)	32 (28- 33)	30 (26- 33)	NA
Birth Weight (grams), median (range)	1235 (750-2000)	1160 (750-1600)	1260 (800-2000)	NA
BW (centile), median (range)	14.45 (0.1- 72.8)	3.33 (0.1- 9.75)	29.59 (10.5-72.8)	NA
Gender				
Male	n=77	31 (40.25%)	46 (59.74%)	NA
Female	n=83	32 (38.56%)	51 (61.44%)	NA
CLINICAL CONDITIONS				
Respiratory Distress Syndrome	n=126	46(36.51%)	80(63.49%)	0.001
Mechanical Ventilation >96h	n=32	9(28.12%)	23(71.78%)	0.001
Surfactant	n=56	16(28.57%)	30(53.57%)	0.001
Caffeine	n=126	46(36.51%)	80(63.49%)	0.00001

Incidence of RDS and interventions done are significantly more in AGA group than SGA neonates as AGA cohort has more premature neonates as compared SGA neonates.

Table 2. Gestational age distribution of AGA and SGA neonates

Gestational age (weeks)	Total (N=160)		SGA (N=63)		AGA (N=97)		P
	Number	%	Number	%	Number	%	
$24^{+0} – 27^{+6}$	11	6.9	0	0.0	11	11.3	NA

28^{+0}-31^{+6}	89	55.6	27	42.9	62	63.9	0.452
32^{+0}-33^{+6}	60	37.5	36	57.1	24	24.7	0.098

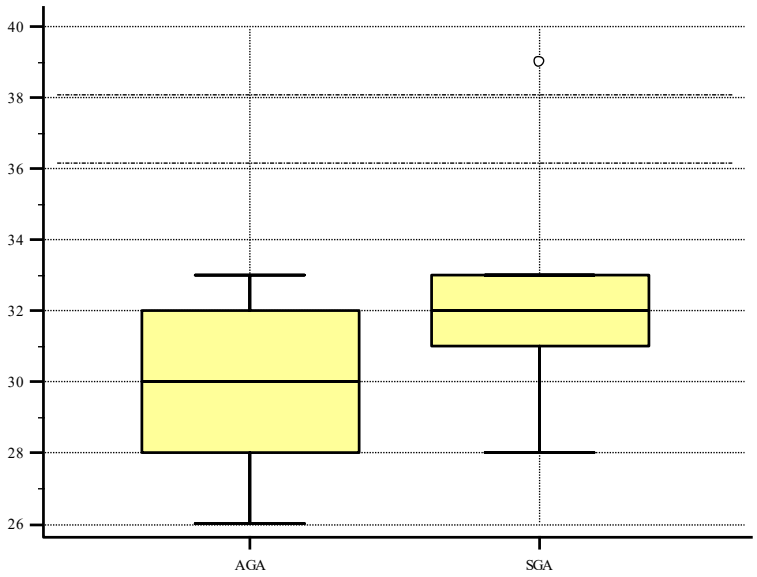

Fig. 1 Box plot of gestational age distribution in SGA and AGA neonates:

Median gestational age in AGA30 weeks (26- 33)and that in SGA is 32 weeks (28- 33).

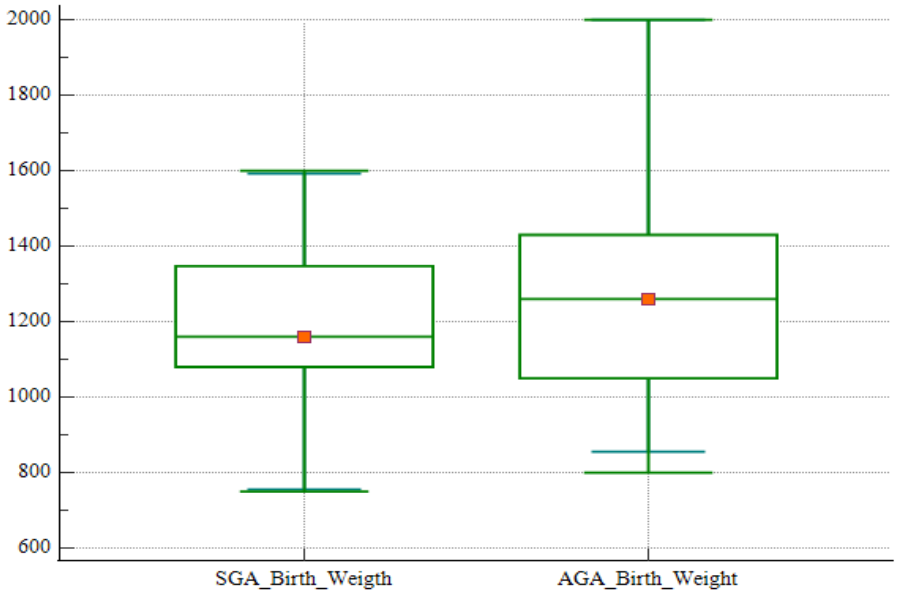

Fig 2. Box plot of birth weight distribution in SGA and AGA neonates:

Median birth weight of 1160 grams (750-1600) in SGA group and 1260 grams (800-2000) in AGA neonates

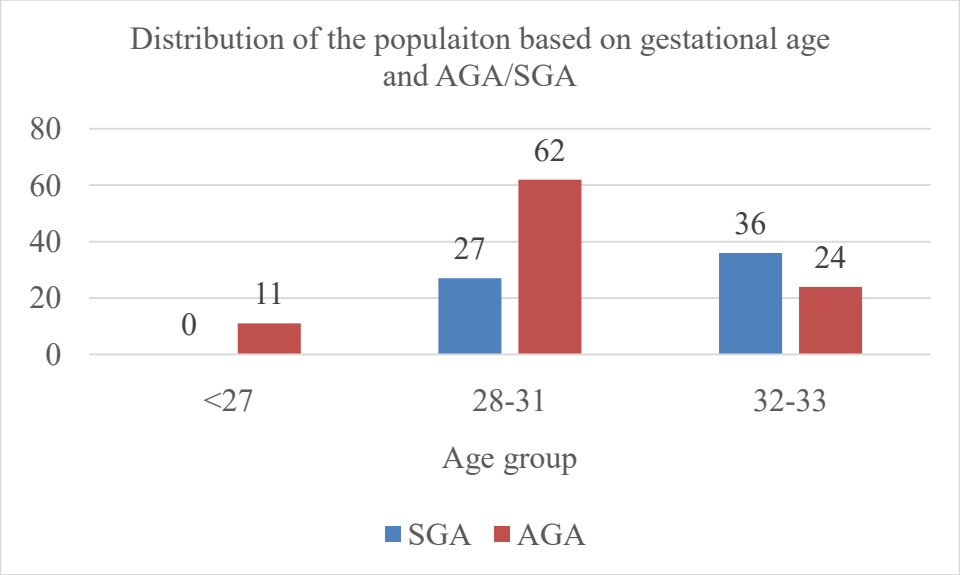

Fig. 3. Histogram of gestational age wise distribution of AGA and SGA neonates:

In this study, Gestational age group (24+0 to 27+6) all 11 neonates were SGA. Gestational age group (28+0 to 31+6) had 27 SGA and 62 AGA neonates; gestational age group (32+0 to 33+6) had 36 SGA and 24 AGA neonates.

Table 3: Univariate Analysis of the factors affecting time to reach full enteral feeds in AGA and SGA neonates:

Parameter	SGA (p-value)	AGA(p-value)
RDS	0.98	1.26
Mechanical ventilation> 96 hours	0.95	0.49
Caffeine	**0.0001**	**0.0001**
Surfactant Administration	**0.022**	**0.001**
RDS: Respiratory Distress Syndrome		

The factors significantly affecting time to reach full enteral feeds in AGA and SGA neonates administration of caffeine and surfactant.

TABLE 4: Multivariate Analysis of factors affecting time to reach full enteral feeds in AGA and AGA neonates:

Parameter	SGA (p- value)	AGA (p- value)
Caffeine	**0.0254**	**0.009**
Mechanical ventilation > 96 hours	**0.001**	**0.000001**

Gestational age	**0.0001**	**0.0001**
RDS	0.35	0.759
Surfactant Administration	**0.001**	**0.001**
RDS: Respiratory Distress Syndrome.		

Factors affecting time to reach full enteral feeds in AGA and SGA are administration of caffeine and surfactant, mechanical ventilation > 96 hours and gestational age. A total 160 neonates were enrolled into study, who were less than 34 completed weeks of gestation. These neonates were further divided into 2 cohorts of SGA and AGA. Every neonate was started on, and graded up enteral feeds according to the standardised institutional preterm enteral feeding protocol. The time required to attain full enteral feeds (@160ml/kg/day) were noted, and factors causing a delay in achieving full feeds were analysed.The perinatal and clinical characteristics have been described in Table 1, 2 and Figs. 1, 2, 3. In our study, of the total enrolled neonates (n=160), 60.6% (n=97) were AGA neonates, while 39.4% % (n=63) were SGA neonates. The median gestational age in the AGA cohort is 30 weeks (Range: 26- 33 weeks), and that in SGA cohort is 32 weeks (Range: 28- 33), with median birth weight of 1260 grams (800-2000g) and 1160 grams (750-1600g) in the AGA and SGA groups respectively. Male neonates constituted 48.12% of the entire cohort (n=77).

However, RDS needing mechanical ventilation (71.8%), surfactant (53.57%)were higher in the AGA cohort (as compared to SGA neonates) indicating a greater level of sickness in this cohort, likely due to greater immaturity in this group. (Table 1). However, 80 neonates in the AGA group (80/97, 82.4%) received caffeine. -In the total cohort of 160 neonates,RDS in 78.75% (20% requiring mechanical ventilation for >96 hours), 78.75% received caffeine and 35% were administered surfactant. In the gestational age category of 24^{+0} – 27^{+6}weeks, there were no SGA neonates in our study, but there was a significant increase in SGA neonates in the 32^{+0}-33^{+6} week group (36/60; 60%).

Discussion:-

The study has been conducted in tertiary care teaching institute, which is the referral institute for many peripheral health care settings. The antenatal high-risk obstetric cases such as pre-eclampsia, eclampsia, multiple gestations, Invitro fertilization cases, chronic maternal illness, abnormal placentation, poor maternal nutrition, maternal infections (TORCH group) and uteroplacental insufficiencies with brain sparing effects etc. are referred to the institute, commonly at onset of labour. The number of high risk antenatal in utero and ex utero referrals may explain the large number of SGA neonates (39.4%) and RDS (78.75%) In a similar study by Bozzetti et al(10), conducted over a 5 year period (2006-2010), 310 infants of gestational age < 32 weeks were studied, and 10.3% (n=32) were SGA neonates and RDS occurred in 178 (57.4%) infants. Incidence of RDS was significantly higher in our study, and could be attributed to poor antenatal steroid cover.

On univariate analysis in our study to assess other factors which could affect TFF, the factors significantly affecting TFF in AGA and SGA neonates were administration of surfactantand caffeine (indicating severity of RDS). Incidence of RDS had no effect on TFF in either of the SGA and AGA cohort. On multivariate analysis in our study to assess other factors which could affect TFF, the factors significantly affecting TFF in AGA and SGA neonates were administration of surfactant and caffeine (indicating severity of RDS) and mechanical ventilation > 96 hours. Incidence of RDS had no effect on TFF in either of the SGA and AGA cohort. In the study conducted by Patwardhan et al(11), on univariate analysis, gestational age and birth weight had an inverse relationship to TFF and RDS had a significant impact on TFF. In the study by Bozzetti et al(10)on univariate analysis, the increase in GA was associated with a reduction in the TFF. Administration of caffeine prolonged time to FEF achievement. We hypothesize that this variation (in the univariate analysis) in the factors causing prolonged TFF, is possibly due to the feeding practices followed by the various authors. While the study by Bozetti(10)and Patwardhan et al(11) were performed in the epochs 2006-2010 and 2014-2016, our study has been more recent with rapid upgrade of feeds in babies provided babies tolerated the feeds. Due to the presence of a milk bank near the NICU in our unit, we were able to give our preterm neonates Mothers own milk (MoM) or pasteurized donor human milk (PDHM), unlike in

the study by Patwardhan(11) where 6.8% of the neonates were administered formula milk. The incidenceof RDS in our study is greater as compared to the studies conducted by Bozetti(10) and Patwardhan et al (11). However, the in our study mere incidence of RDS had no effect on TFF. The interventions done for the RDS indicating the severity such as mechanical ventilation >96 hours, administration of surfactant and caffeine prolonged the TFF.

Conclusion:-

In this study, factors significantly impacting the time to reach full enteral feeds in SGA and AGA group were gestational age,surfactant and caffeine administration and mechanical ventilation >96 hours. Overall incidence of RDS did not significantly affect time to reach full feeds in either of the two groups.

Bibliography:-

1.Lee AC, Kozuki N, Cousens S, Stevens GA, Blencowe H, Silveira MF, et al. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21st standard: analysis of CHERG datasets. BMJ. 2017 Aug 17;358:j3677.
2.Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron M, et al. Intrauterine, Early Neonatal, and Postdischarge Growth and Neurodevelopmental Outcome at 5.4 Years in Extremely Preterm Infants After Intensive Neonatal Nutritional Support. Pediatrics. 2009 Jan 1;123(1):e101–9.
3.Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm Birth: Causes, Consequences, and Prevention [Internet]. Behrman RE, Butler AS, editors. Washington (DC): National Academies Press (US); 2007 [cited 2020 Nov 26]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK11362/
4. Cassir N, Simeoni U, La Scola B. Gut microbiota and the pathogenesis of necrotizing enterocolitis in preterm neonates. Future Microbiol. 2016;11(2):273–92.
5. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. Neonatology. 2017;111(2):107–25.
6. dos Santos Mezzacappa MAM, Collares EF. Gastric Emptying in Premature Newborns with Acute Respiratory Distress. J Pediatr Gastroenterol Nutr. 2005 Mar;40(3):339–44.
7. Bhatia J. Current options in the management of apnea of prematurity. Clin Pediatr (Phila). 2000 Jun;39(6):327–36.
8.Cox C, Hashem NG, Tebbs J, Bookstaver PB, Iskersky V. Evaluation of caffeine and the development of necrotizing enterocolitis. J Neonatal-Perinat Med. 2015;8(4):339–47.
9. Gounaris AK, Grivea IN, Baltogianni M, Gounari E, Antonogeorgos G, Kokori F, et al. Caffeine and Gastric Emptying Time in Very Preterm Neonates. J Clin Med. 2020 Jun;9(6):1676.
10. Bozzetti V, Paterlini G, DeLorenzo P, Meroni V, Gazzolo D, Bel FV, et al. Feeding tolerance of preterm infants appropriate for gestational age (AGA) as compared to those small for gestational age (SGA). J MaternFetal Neonatal Med. 2013 Nov 1;26(16):1610–5.
11. Patwardhan G, Soni A, Rachwani N, Kadam S, Patole S, Pandit A. Factors Associated with Time to Full Feeds in Preterm Very Low Birth Weight Infants. J Trop Pediatr. 2018 Dec 1;64(6):495–500.