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Original Research Article

Risk factors for extrauterine growth restriction in preterm neonates: a prospective analytical cohort study

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ABSTRACT

Background: Objective of the study was to determine the incidence and risk factors for extrauterine growth restriction (EUGR) at discharge in preterm neonates.
Methods: This prospective analytical cohort study included 107 preterm neonates between 30-35 weeks of gestational age who were admitted to a tertiary neonatal intensive care unit from January 2016 to December 2016. These preterm neonates were classified into EUGR group (n=93) and non-EUGR group (n=14) based on the body weight at discharge. The risk factors for EUGR were analyzed statistically.
Results: The incidence of EUGR at discharge was 87.4% in the cohort. Delay in initiation of parenteral nutrition (p=0.04), longer time to reach full enteral feeds (p=0.03), very low birth weight (p=0.01), small for gestational age (p=0.01), intrauterine growth restriction (p=0.01), necrotizing enterocolitis (p=0.03), late-onset sepsis (p=0.03) and bronchopulmonary dysplasia (p=0.04) were significant risk factors for extra-uterine growth restriction at discharge in preterm neonates.
Conclusions: The incidence of EUGR can be decreased by improving perinatal care, minimizing preterm deliveries, early initiation of parenteral nutrition and enteral feeding and reducing immediate postnatal complications.

Keywords: Extrauterine growth restriction, Preterm, Incidence, Risk factors, Feeding, Sepsis

INTRODUCTION

Extrauterine growth restriction (EUGR) is a medical problem with long term health consequences into infancy and childhood.[1,2] Despite a lot of changes in the nutritional interventions in the neonatal intensive care units, significant proportion of babies especially preterm infants show EUGR. Preterm infants are commonly diagnosed as having EUGR when weight at discharge or around 36–40 weeks postpartum age is below the 10th percentile.[3,4] Studies have demonstrated the association between EUGR and an increased morbidity and mortality in the neonatal period and its influence on neurodevelopmental outcomes in very preterm babies.[5-7] The burden of EUGR is variable in developed and developing countries. This study was conducted to estimate the incidence of EUGR in preterm neonates and to determine the risk factors associated with it.

METHODS

This prospective cohort study was conducted at King Edward Memorial Hospital, Pune from January 2016 to December 2016. Purposive sampling method was employed in this study wherein all preterm babies between 30 weeks of gestational age to 35 weeks of gestational age were enrolled. Those with major congenital anomaly, surgical conditions of abdomen, genetic/chromosomal disease or died before discharge were excluded from the study. Written informed consent was obtained from the parents. This study was approved by institutional review board and ethics committee. The primary objective was to

estimate the incidence of EUGR and the secondary objective was to identify risk factors for EUGR in preterm neonates.

Baseline demographic characteristics were recorded and entered into a case record form. Growth was assessed by recording anthropometry at birth and was compared with anthropometric parameters taken at discharge. Depending on the discharge anthropometric measurements, the enrolled preterm neonates were assigned to either "EUGR group" or "non-EUGR group". Factors like gestational age (estimated by new Ballard score, menstrual history and/or from results of first trimester ultra-sonographic examination), birth weight, duration of parenteral nutrition, initiation and duration of enteral feeding, respiratory support, time to reach full enteral feeds, duration of neonatal intensive care unit (NICU) stay, antenatal growth restriction, gender, feeding intolerance, necrotizing enterocolitis, hemodynamically significant patent ductus arteriosus, chronic lung disease, early onset and late-onset sepsis were compared in the 2 groups to identify the factors associated with EUGR in preterm babies.

Statistical analysis

Data were entered in Microsoft excel and analyzed using stata version 13.1 (StataCorp, College Station, Texas, USA). We calculated the mean and standard deviation, and median and interquartile ranges for the linear variables and proportions for the categorical variables. The mean between two groups was compared using the unpaired and paired t-test (for different groups, and pre-and post-means respectively). We used the Mann-Whitney two sample statistics for non-parametric data. The proportions were compared using the Chi square test or the Fisher's exact test (for low expected cell counts). A p value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of 138 preterm neonates were eligible for the study, out of which 25 died before discharge and 6 neonates were shifted to other hospital. One hundred and seven (n=107) preterm neonates were enrolled in the study and followed up longitudinally till discharge from the hospital. At discharge, 87.4% (n=93) of the enrolled neonates were having EUGR as compared to 12.6% (n=14) enrolled neonates who had normal growth parameters at discharge. Parenteral nutrition was started in EUGR babies at a mean 13.7 (±3.5) hours of life and in non-EUGR babies at mean 10.8 (±2.3) hours of life (p=0.04). The mean duration of PN in EUGR and non-EUGR babies was 7.1 (±4.9) days and 5.7 (±2.9) days, respectively (p=0.09). The mean time to start enteral feeding was 1.9 (±1.2) days in EUGR group and 2.1 (±0.5) days in non-EUGR group, respectively (p=0.16) while EUGR group babies took a mean of 12.7 (±7.4) days to reach full enteral feeds in comparison to non-EUGR babies who took only 8.2 (±4.4) days to achieve full feeds (p=0.03). The mean gestational age at birth was 31.9 (±1.9) weeks and 32.8 (±2.2) weeks in EUGR group and non-EUGR group, respectively (p=0.33). The mean birth weight was 1185.3 (±236.8) grams in EUGR group as compared to a mean of 1392.9 (±316.3) grams in non-EUGR group (p=0.01). The mean duration of NICU stay was 33.6 (±20.4) days and 29.2 (±18.3) days in EUGR group and non-EUGR group, respectively (p=0.12). These characteristics are shown in Table 1.

In EUGR group, 68.8% (n=64) babies developed feeding intolerance as compared to 71.4% (n=10) babies in non-EUGR group (p=0.68). Among EUGR group, 73.1% (n=68) babies were born intramurally as compared to 71.4% (n=10) who were transferred-in to our unit from other hospitals (p=0.50). Male gender was not associated with EUGR at discharge in this study (p=0.14). AGA babies were less likely to develop EUGR at discharge (p=0.04). In EUGR group, 66.6% (n=62) of the babies were small for gestational age at birth as compared to 14.3% (n=2) of babies in non-EUGR group, which was statistically significant (p=0.01) while 45.2% (n=42) babies were growth restricted in antenatal scans in EUGR group in comparison to 14.3% (n=2) in non-EUGR group (p=0.01). NEC developed in 8.6% (n=8) of babies in EUGR group whereas none of the babies in non-EUGR group had NEC (p=0.03). These characteristics are shown in Table 2.

Mean duration of CPAP support in EUGR group was 6.7 (±2.9) days and 5.5 (±1.8) days in non-EUGR group which was not statistically significant (p=0.55). In EUGR group, 29.1% (n=27) babies had Apgar score <7 at five minute in comparison to 35.7% (n= 5) babies with Apgar score <7 at five minutes (p=0.09). Hemodynamically significant PDA was present in 24.7% (n=23) babies in EUGR group and in 21.4% (n=3) babies in non-EUGR group (p=0.42). In EUGR group, EOS was present in 10.8% (n=10) of babies while same was present in 7.1% (n=1) of babies in non-EUGR group (p=0.33). LOS was present in 32.3% (n=30) of babies in EUGR group and 21.4% (n=3) of babies in non-EUGR group, which was statistically significant (p=0.03). In EUGR group, BPD was present in 12.9% (n=12) of babies in comparison to 7.1% (n=1) babies in non-EUGR group, which was statistically significant (p=0.04). The morbidity data is shown in Table 3.

Table 1: Baseline characteristics in EUGR and non-EUGR group.

Variable	EUGR group (n=93) Mean (±SD)	Non-EUGR group (n=14) Mean (±SD)	P value
Initiation of PN (hours)	15.7 (±3.5)	8.8 (±2.3)	0.04
Duration of PN (days)	7.1 (±4.9)	5.7 (±2.9)	0.09

Continued.

Variable	EUGR group (n=93) Mean (±SD)	Non-EUGR group (n=14) Mean (±SD)	P value
Initiation of feeding (days)	1.9 (±1.2)	2.1 (±0.5)	0.16
Time to full feeds (days)	12.7 (±7.4)	8.2 (±4.4)	0.03
Gestational age (weeks)	31.9 (±1.9)	32.8 (±2.2)	0.33
Birth weight (grams)	1185.3 (±236.8)	1392.9 (±316.3)	0.01
NICU stay (days)	33.6 (±24.4)	29.2 (±27.3)	0.12

Table 2: Characteristics of EUGR group and non-EUGR group.

Variable	EUGR (n=93) n (%)	Non-EUGR (n=14) n (%)	P value
Feed intolerance	64 (68.8)	10 (71.4)	0.68
Male gender	49 (52.7)	8 (57.1)	0.14
Intramural delivery	68 (73.1)	10 (71.4)	0.50
Appropriate for gestational age	31 (33.3)	12 (85.7)	0.04
Small for gestational age	62 (66.6)	2 (14.3)	0.01
Intra-uterine growth restriction	42 (45.2)	2 (14.3)	0.01
Necrotizing enterocolitis	8 (8.6)	0 (0)	0.03

Table 3: Morbidity in EUGR group and non-EUGR group.

Morbidity	EUGR (n=93) n (%)	Non-EUGR (n=14) n (%)	P value
Apgar score <7 at 5 minute	27 (29.1)	5 (35.7)	0.09
hs patent ductus arteriosus	23 (24.7)	3 (21.4)	0.42
Early onset sepsis	10 (10.8)	1 (7.1)	0.33
Late onset sepsis	30 (32.3)	3 (21.4)	0.03
Bronchopulmonary dysplasia	12 (12.9)	1 (7.1)	0.04

DISCUSSION

The etiology of EUGR is multifactorial. The incidence of EUGR depends on the definition used for defining EUGR and growth charts used to compare and calculate. There are many reasons for postnatal growth failure among preterm infants that are not directly related to nutritional support. Many of these infants are critically ill with significant pathological stresses that reduce anabolic capacity and growth—surgery, infections, necrotizing enterocolitis (NEC), hypoxic–ischemic conditions with or without actual injuries, acute and chronic lung disease.[8,9] An underlying feature of most is inflammation, which frequently is systemic, and almost invariably produces cytokines that interfere with normal anabolic processes. Anemia of prematurity, primarily caused by phlebotomy for hematological and biochemical tests required to diagnose and follow adverse conditions, leads to lower than normal blood oxygen content, which limits anabolism.[10] Respiratory support with ventilators and high oxygen concentrations also cause pulmonary and systemic inflammation.[11] Antibiotics produce an abnormal gut microbiome, which leads to poor nutrient digestion and absorption, and has been associated with development of NEC. Embleton et al reported that nutrient intake explained 45% of the variation in growth performance, the effects of birth weight explained 7%, and the rest was attributable to non-nutritional factors.[12]

EUGR was present in 87% of preterm babies at discharge in this study. The incidence of EUGR is reported high (50-94%) in developing countries and it correlates inversely with gestational age.[13] A study from north India observed the incidence of EUGR was 64.8% at discharge and 76.8% at term.[14] NICHD network found an incidence of 97% of EUGR in very low birth weight babies at discharge and 40% of these were having weight still less than 10th centiles at 18 months of age.[15] A similar study in West Australia in 2010 has observed an incidence of 50% of EUGR at discharge in babies <28 weeks of gestational age.[13] Ehrenkranz et al in their study observed a EUGR incidence of 26% at discharge considering weight centile and 5% when considering head circumference centile.[16] In a Korean study, the frequency of EUGR at discharge was 67%.[17] A Chinese study found a EUGR incidence of 49.7% considering weight centile and 23.1% when considering head circumference centile.[18] Same study showed incidence of EUGR in very low birth weight (VLBW) infants as 78.9% and 50.0% when assessed by weight and head circumference centiles, respectively.[18] Another Chinese study by Zhonghua et al has found a EUGR incidence at discharge of 60.0%, 58.9% and 29.5% when assessed on the basis of weight, length and head

circumference centiles respectively.[19] It should be noted that the use of different intrauterine growth curves by these investigators contributed to the variability in the incidence of EUGR.[16]

Studies have shown that EUGR is associated with gestational age at birth. Shan et al stated that gestational age at birth was related to EUGR and also has effect on head circumference and weight at discharge.[18] Study by Sakurai et al found that lower gestational age was contributing to EUGR incidence at discharge for weight, length, and head circumference.[20]

The mean birth weight of babies in EUGR group was smaller than the babies in non-EUGR group in our cohort. These findings were in agreement with Shan et al. where they observed that the incidence of EUGR increased with the decreasing birth weight.[2] An American study determining predictors of EUGR showed that infants who developed EUGR had significantly lower birth weights at birth.[12] In a Korean study, birth weight was independent predictor of EUGR at discharge.[17] Similar study from China observed that lower the birth weight, the higher is the incidence of risk of EUGR at discharge.[21]

In our study, even 33.3% of the babies who were AGA at birth developed EUGR at discharge. EUGR at discharge was more common in SGA babies in our cohort. This was in agreement with the study by Ehrenkranz et al in which they have demonstrated that the babies who were SGA at birth are at higher risk of being EUGR at discharge.[16] A study by Lima et al observed that 54.2% of the SGA infants had EUGR at discharge considering weight and 7.4% considering HC, while only 12.3% of the AGA infants had EUGR at discharge considering weight and 4% considering HC.[22]

In our study, NEC developed in 8.6% of babies in EUGR group. Incidence of NEC as per weight of baby was found to be is 3% in 500-750 grams, 3% in 750-1000 grams, 3% in 1000-1250 grams and 2% in 1250-1500 grams. NEC depends upon various ante partum, intrapartum and postpartum factors causing the difference. Also definition of medical NEC and feed intolerance is overlapping, so it might be underreported.[23]

Our study did not find any predilection for male gender developing EUGR at discharge. However, the study by Ehrenkranz et al demonstrated that male gender was significantly associated with a lower weight z score at hospital discharge.[16] Study by Shan et al also showed that gender of the baby had bearing on EUGR.[18]

Intra-uterine growth restriction (IUGR) on antenatal USG was a significant risk factor for EUGR in preterm neonates at discharge in our cohort. Studies done by Ehrenkranz et al and Sakurai et al also observed that IUGR was an important risk factor for EUGR at discharge.[16,20]

Delay in starting parenteral nutrition was a significant risk factor for being EUGR at discharge in preterm babies in our cohort. A study conducted in United States found that the duration of parenteral nutrition was an independent predictor of developing EUGR at discharge.[12]

Though both EOS and LOS were higher in EUGR group but only LOS was significantly associated with EUGR at discharge in preterm babies in this study. In a study, Radmacher et al observed that sepsis was more commonly found in EUGR babies.[12] Another study by Ehrenkranz et al observed that LOS was independently associated with EUGR at discharge.[16]

Bronchopulmonary dysplasia was a significant risk factor for EUGR at discharge in this study. This observation was in agreement to the findings by Ehrenkranz et al and Radmacher et al.[7,12] Sakurai et al also found that severe BPD was a significant risk factor for EUGR.[20]

Incidence of hsPDA was more in EUGR group in our cohort, but it was not statistically significant. However, a study by Ehrenkranz et al observed that hsPDA was a significant risk factor for EUGR at discharge, which might be because our study could have been under-powered to detect the association between hsPDA and EUGR.[16]

CONCLUSION

Delay in initiation of parenteral nutrition, longer time to reach full enteral feeds, very low birth weight, small for gestational age, intrauterine growth restriction, necrotizing enterocolitis, late-onset sepsis and bronchopulmonary dysplasia were significant risk factors for extra-uterine growth restriction at discharge in preterm neonates. The incidence of EUGR can be decreased by improving perinatal care, minimizing preterm deliveries, early initiation of parenteral nutrition and enteral feeding and reducing immediate postnatal complications. Appropriate interventions should be adopted to minimize these risk factors to improve the growth and development of preterm neonates.

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