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Extra uterine growth restriction and its related factors in extremely and very low birth weight babies including 1500 grams admitted to Jammhoria hospital in Benghazi.

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Original Research Article

Abstract

Background:Extra-uterine growth restriction (EUGR) in premature infants remains a major challenge for neonatologists worldwide. In the neonatal intensive care unit (NICU), suboptimal nutrition and the fear of advancing feeds are key contributors. Updated feeding protocols that support rapid but safe feeding advancement, breast milk fortification, and close monitoring of growth parameters are essential to achieving optimal nutritional outcomes and preventing long-term neurodevelopmental impairment.

Objective: To determine the frequency of extra-uterine growth restriction (EUGR) among premature infants in Benghazi and identify associated risk factors.

Method: This cross-sectional study was conducted in Benghazi. Medical records of 107 premature infants were obtained from the neonatal clinic. All preterm infants born at <34 weeks' gestation and weighing ≤1500 grams were included. Growth measurements at birth, discharge, and 40 weeks corrected age were plotted on Fenton growth charts. Weight <10th percentile was classified as EUGR. A p-value <0.05 was considered statistically significant.

Results: EUGR was identified in 85 infants (79%) at discharge and in 63 infants (58.8%) at 40 weeks corrected age. Significant risk factors for EUGR at discharge and at 40 weeks included lower birth weight (p = 0.01; p = 0.005), longer hospital stay (p = 0.007; p = 0.01), small for gestational age (SGA) (p = 0.000; p = 0.02), and sepsis (p = 0.03; p = 0.001). Additionally, gestational age 33–34 weeks (p = 0.001) and multiple births (p = 0.03) were significant risk factors for EUGR at discharge only.

Conclusion: Extra-uterine growth restriction is highly prevalent among Libyan premature infants. Lower birth weight, prolonged hospitalization, SGA status, gestational age of 33–34 weeks, and multiple births were significant associated risk factors.

Recommendations: Implementation of updated feeding protocols for premature infants in Libya—including rapid but safe advancement of enteral feeds, breast milk fortification, and close monitoring of growth parameters—is essential to improving nutritional outcomes and reducing the risk of EUGR.

Keywords: Benghazi, extra-uterine growth restriction, extremely low birth weight, very low birth weight, premature infants.

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INTRODUCTION

The survival rate of extremely and very low birth weight infants has improved significantly in recent years, largely due to advances in neonatal medical care, including enhanced respiratory and nutritional support (1,2). However, suboptimal nutrition remains a major challenge in many Neonatal Intensive Care Units (NICUs) worldwide, often leading to extra-uterine growth restriction (EUGR) among premature infants.

EUGR is defined as weight, head circumference, or length ≤10th percentile of intrauterine growth expectations, assessed at discharge, 36 weeks, or 40 weeks corrected age (3). Major neonatal societies—including the American Academy of Pediatrics, the Canadian Pediatric Society, and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)—recommend that postnatal growth in preterm infants should approximate intrauterine growth rates, ensuring that growth at corrected age is comparable to that of term infants.

A number of factors contribute to this largely irreversible condition. Suboptimal early nutrition, particularly inadequate protein intake in the first weeks of life, is considered one of the most important contributors (4). Other independent risk factors associated with EUGR include intrauterine growth restriction (IUGR), need for assisted ventilation on the first day of life, prolonged respiratory support for more than 28 days, male sex, extended hospitalization, development of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), sepsis, exposure to steroids during hospitalization, delayed return to birth weight, and delayed achievement of full enteral feeds (3,5–7).

Over the last 10–15 years, nutritional guidelines have been refined to reduce the risk of EUGR, and these updates have shown promising outcomes. Current recommendations support early and aggressive initiation of both parenteral and enteral nutrition, with progressive advancement to full enteral feeds (8–11). These approaches have been associated with earlier recovery of birth weight, improved weight at discharge, shorter duration of parenteral nutrition, earlier attainment of full feeds (8,11), lower rates of late-onset sepsis, and reduced incidence of NEC (9,12). Furthermore, milk fortification—whether human milk fortifiers or preterm formulas—along with post-discharge nutritional support provides an opportunity for catch-up growth (13).

Recent findings demonstrate that fortification of breast milk, close monitoring of growth parameters, and adherence to consensus guidelines from major neonatal societies can enable preterm infants to achieve growth trajectories that align with their birth percentiles. ESPGHAN has also introduced updated recommendations for targeted nutrition during critical illness, emphasizing optimal protein and energy delivery to support appropriate growth (14). In Japan, breast milk fortification standards were enhanced in the 2010s, and updated enteral feeding guidelines were introduced in 2017 (15).

EUGR is associated with poor neurodevelopmental outcomes, with long-term and often irreversible consequences (16,17). With the advancement of digital technologies, machine learning (ML) and artificial intelligence (AI) have been applied to better understand factors influencing EUGR. For example, Bozzetti et al. used ML to identify clinical and nutritional predictors of EUGR among infants born before 33 weeks and demonstrated the strong predictive value of early clinical and nutritional variables (18).

In Libya, the absence of standardized feeding guidelines—combined with reluctance among some clinicians to initiate early and aggressive feeding in extremely low and very low birth weight or critically ill infants—contributes to a higher risk of EUGR. Although national nutritional strategies were launched in 2020, implementation remains challenging, particularly in the care of sick premature infants. This study aims to highlight the magnitude of this problem in Benghazi and to raise awareness of the need for urgent improvements in nutritional practices for premature infants.

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AIM of THE STUDY

-To estimate the frequency of extra-uterine growth restriction (EUGR) at discharge and at 40 weeks corrected age among extremely and very low birth weight premature infants (≤1500 grams).

-To identify the clinical characteristics and postnatal factors significantly associated with EUGR in premature infants ≤1500 grams.

METHODOLOGY

It is a cross-sectional study that included 107 premature babies who were discharged from the NICU (neonatal intensive care unit) in Jammhoria Hospital in Benghazi. It is a public maternity hospital where extremely low, very low, and low birth weights (≤ 1500 grams) were born in Benghazi. We selected 107 premature babies who were attending the neonatal clinic for follow-up and for their growth assessment, with inclusion criteria that included premature babies ≤ 34 weeks gestation with birth weight ≤ 1500 grams, and excluded premature babies with congenital anomalies and those babies without recorded data for weight and head circumference at both discharge and corrected age. We collected their files selectively from the neonatal clinic according to inclusion criteria during the period from 2004 until 2015. We collected the data from the files, which include their weight and head circumference at birth, weight at discharge, and at 40 weeks corrected age; their gestational age; sex; duration of hospital stay; and type of pregnancy (single or multiple births). The related factors that may predispose to EUGR were also registered, including the use of a ventilator or bubble non-invasive continuous positive pressure (CPAP), a history of hyaline membrane disease (HMD), necrotizing enterocolitis, a history of apnea, sepsis, bronchopulmonary dysplasia (BPD), and a maternal history of hypertension or preeclampsia. The measurements of birth weight were plotted on the Fenton chart; according to that, we divided them into 2 groups: group of average gestational age (AGA) for those with birth weight > 10th centile, another group of small for gestational age (SGA) with birth weight ≤ 10th centile, and then the weight at discharge and at 40 weeks corrected age were again plotted on charts. Those babies with weight at discharge and 40 weeks corrected age ≤ 10th were defined as babies with extra-uterine growth restriction (EUGR). The two groups of AGA and SGA were compared for the frequency of EUGR, and both groups of EUGR and non-EUGR at discharge and 40 weeks were compared with certain factors that may predispose to EUGR that involved:

Clinical characteristics included sex, birth weight, gestational age, weight for gestational age (either SGA or AGA), duration of hospital stay, and type of pregnancy. Postnatal factors included use of a ventilator or CPAP, a history of hyaline membrane disease (HMD), necrotizing enterocolitis (NEC), a history of apnea, sepsis, BPD, and a history of maternal hypertension or preeclampsia.

DATA ANALYSIS

The preterm infants were categorized into two groups: extra-uterine growth restriction (EUGR) and non-extra uterine growth restriction (non-EUGR). Quantitative data were summarized using descriptive statistics, including mean (M), median (Mdn), and standard deviation (SD). To assess the associations between variables and EUGR status at discharge and 40 weeks corrected age, inferential statistical tests were employed. Categorical variables were analyzed using the chi-square test (χ^2) or Fisher's exact test, as appropriate, while continuous variables were evaluated using the independent samples t-test. A two-sided significance level of $\alpha = 0.05$ was adopted, with p-values < 0.05 deemed statistically significant. All statistical analyses were performed using IBM SPSS Statistics, Version 23 (19).

ETHICAL CONSIDERATIONS

Verbal approval to conduct the study was obtained under the supervision of the Neonatal Department and the neonatal follow-up clinic

RESULTS

In the study, 107 premature babies between the period of 2004 and 2015 whose gestational age was 34 weeks or less with a birth weight of ≤ 1500 grams. Out of them, 73 (68.2%) were female, and the ges-

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tational age between 28 and 32 weeks was estimated in 67.2%; the minimum gestational age was 28 weeks. The mean head circumferences at birth, at discharge, and at 40 weeks were 27.8±1.7, 28±1.39, and 33.59±2, respectively. The birth weight for most of them (63.6%) was between 1200 and 1500 grams; the minimum birth weight was 0.635 kg; the mean birth weight was 1250 grams. (Table 1) (Figure. 1).

Table (1): Descriptive statistics of clinical characteristics for premature babies

Characteristics of study participants	Descriptive statistics				
	Mean	Standard deviation	Median	Minimum	Maximum
Gestational Age in weeks	31.53	1.61	31	28	34
Duration of stay at hospital in days	14.4	9.90	11	1	55
Birth Weight in kg	1.25	0.168	1.28	0.635	1.5
Weight at discharge in kg	1.23	0.885	1.24	0.885	1.600
Weight at corrected age in kg	2.63	0.682	2.6	1.070	4.100
Head circumference at birth in cm	27.81	1.71	28	21.8	33
Head circumference at corrected age in cm	33.59	2.019	34	29	39

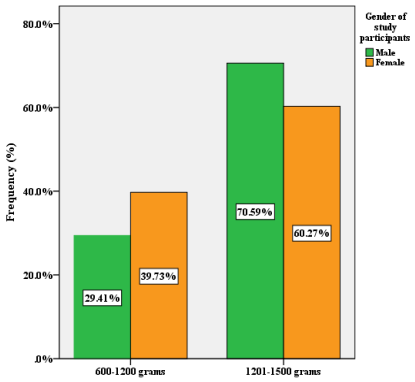

Figure.1: Distribution of premature babies by their birth weight.

The duration of stay at the hospital for 79.4% of premature babies was 1-20 days (Fig. 2). Almost all premature babies (59%) had a birth weight that was average for gestational age (AGA); it means that their birth weight was above the 10th centile. The pregnancy was single in 70.1% (Table 2).

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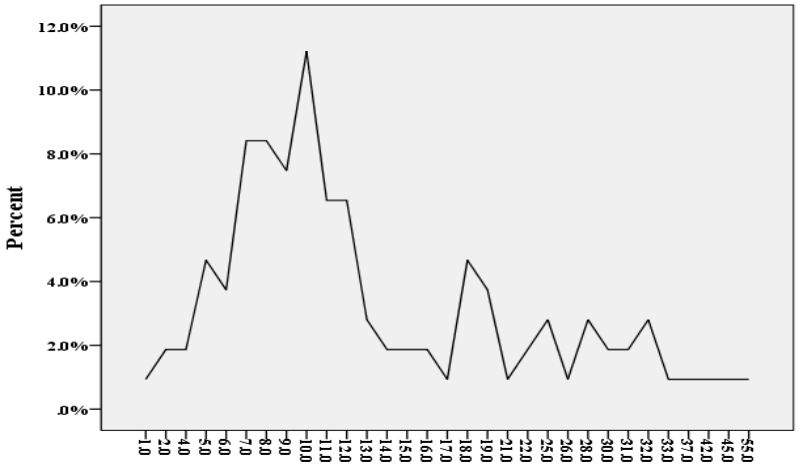

Figure 2: Duration of hospital stay for premature babies

Table (2): Clinical characteristics of extremely and very low birth weight babies ≤ 1.5kg and with ≤ 34 weeks

Clinical characteristics		Frequency	%
Sex	Male	34	31.8
	Female	73	68.2
Gestational weeks	28-30	36	33.6
	31-32	36	33.6
	33-34	35	32.7
Birth weight (kg)	0.600-1.2	39	36.4
	1.201-1.5	68	63.6
Weight for gestational age	SGA	44	41.1
	AGA	63	58.9
Duration of hospital stay (days)	1-20	85	79.4
	21-60	22	20.6
Type of pregnancy	Single	75	70.1
	Twin	24	22.4
	Triplets and quadruplets	8	7.4

There were a lot of morbidities that can contribute to extrauterine growth restriction in the study group listed in Table 3, including hyaline membrane disease (HMD), which was represented in 77.6% of premature infants.

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Table (3): Postnatal factors among premature babies

Clinical characteristics		Frequency	%
HMD Missed 2 cases	Yes	83	77.6
	No	22	20.6
Sepsis	Yes	23	21.5
	No	84	78.5
NEC	Yes	6	5.6
	No	101	94.4
ventilator support	Yes	6	5.6
	No	101	94.4
Bubbling CPAP	Yes	45	42.1
	No	62	57.9
Apnoea	Yes	19	17.8
	No	88	82.2
BPD	Yes	1	0.9
	No	106	99.1
Maternal hypertension Missed 64 cases	Yes	24	22.4
	No	19	17.8

-The estimation of EUGR in our study was at two groups of age: at discharge and 40 weeks corrected age. A total of 85 (79%) of infants had EUGR at discharge (Figure. 3), compared to 63 (58.8%) of premature babies who had EUGR at 40 weeks (Figure. 4).

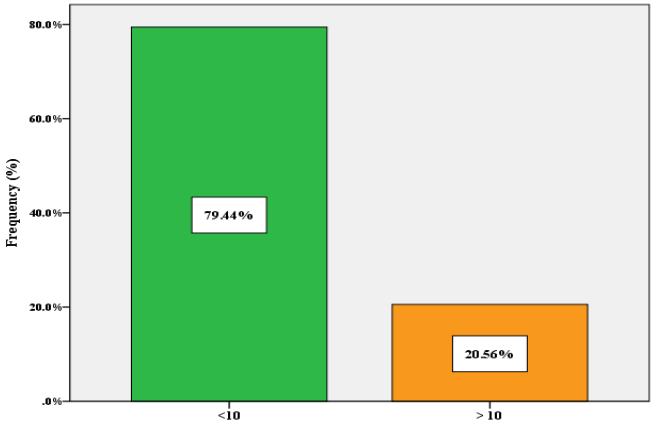

Figure.3: Frequency of EUGR according to weight at discharge

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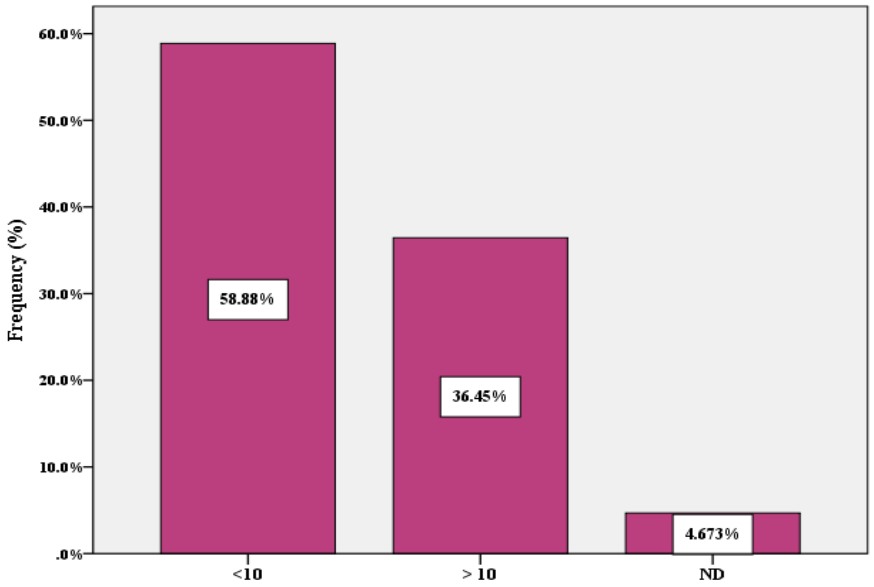

Figure.4: Frequency of EUGR according to weight at 40-week corrected age

Clinical characteristics of EUGR and non-EUGR at discharge: The females were more in the EUGR group (57) than the males, but the sex was negatively correlated to EUGR. Significant differences between EUGR and NON-EUGR groups were identified for the smaller birth weight (SGA) (p=0.000), longer stay in hospital (p=0.007), lower birth weight (p=0.01), premature birth from multiple pregnancy (p=0.03) (whether twin, triplets, or quadruplets), and 33-34 gestational weeks (p=0.001). All were statistically related to EUGR (Table 4).

Table (4): Association between clinical characteristics and EUGR at discharge:

Clinical characteristics		EUGR	No EUGR	X^2	P-value
Sex	Male	28	6	0.259	0.611
	Female	57	16		
Gestational weeks	28-30	23	13	14.823	0.001**
	31-32	27	9		
	33-34	35	0		
Birth weight (kg)	0.600-1.2	36	3	6.222	0.01**
	1.201-1.5	49	19		
Weight for gestational age	SGA	44	0	19.342	0.000**
	AGA	41	22		
Duration of hospital stay(days)	1-20	63	22	7.168	0.007**
	21-60	22	0		
Type of pregnancy	Single	59	16	6.46	0.03**
	Twin	22	2		
	Triplets and quadruplets	4	4		

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The clinical characteristics of EUGR and non-EUGR at 40 weeks: smaller for gestational age (SGA) (p=0.02), lower birth weight (p=0.005), and longer stay in hospital (p=0.01) were significantly associated with EUGR. whereas sex, gestational age, and multiple gestation were negatively correlated to EUGR (Table 5).

Table (5): Association between clinical characteristics and EUGR at 40 weeks corrected ages

Clinical characteristics		EUGR	No EUGR	X^2	P-value
Sex	Male	23	10	1.64	0.439
	Female	40	29		
Gestational weeks	28-30	21	11	5.886	0.208
	31-32	20	15		
	33-34	22	13		
Birth weight	0.600-1.2	31	7	10.77	0.005**
	1.201-1.5	32	32		
Weight for gestational age	SGA	32	12	7.653	0.02**
	AGA	31	27		
Duration of hospital stay	1-20	44	37	9.241	0.01**
	21-60	19	2		
Type of pregnancy	Single	43	4	4.24	0.374
	Twin	17	0		
	Triplets and quadruplets	3	1		

Postnatal risk factors for EUGR at discharge and 40 weeks corrected age: there was a significant association between EUGR and history of sepsis at discharge and at 40 weeks ($X^2 = 4.715$, $p = 0.03$) and ($X^2 = 13.52$, $p = 0.001$), respectively (Table 6) (Table 7).

Table (6): Association between the postnatal risk factors and EUGR at discharge:

Risk factors		EUGR	No EUGR	X^2	P-value
HMD Missed 2 cases	Yes	64	19	0.899	0.343
	No	19	3		
sepsis	Yes	22	1	4.715	0.03**
	No	63	21		
NEC	Yes	5	1	0.059	0.808
	No	80	21		
ventilator support	Yes	6	0	1.645	0.200
	No	79	22		
Bubbling CPAP	Yes	34	11	0.717	0.397
	No	51	11		
Apnoea	Yes	17	2	1.424	0.233
	No	68	20		
BPD	Yes	1	0	0.261	0.609
	No	84	22		
Maternal hypertension Missed 64 cases	Yes	18	6	5.028	0.08
	No	12	7		

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Table (7): Association between the postnatal risk factors and EUGR at 40 weeks corrected ages

Risk factors		EUGR	No EUGR	X^2	P-value
HMD	Yes	50	29	0.270	0.874
	No	12	9		
Sepsis	Yes	21	1	13.52	0.001**
	No	42	38		
NEC	Yes	5	1	1.625	0.444
	No	58	38		
ventilator support	Yes	4	2	0.379	0.827
	No	59	37		
Bubbling CPAP	Yes	30	13	2.026	0.363
	No	33	26		
Apnoea	Yes	14	4	2.380	0.304
	No	49	35		
BPD	Yes	1	0	0.705	0.703
	No	62	39		
Maternal hypertension	Yes	15	8	6.97	0.137

DISCUSSION

Our study evaluated how much the EUGR was a frequent challenge between our premature babies, especially those who were extremely and VLBW babies, and for associated clinical characteristics and morbidities as risk factors for EUGR.

Females were most frequent in the study group of premature babies, most of them with smaller gestational ages of 28-32 weeks. The females and the mean gestational age in our study are exactly the same as those in the study done in Ethiopia by Gidi et al. (20). However, in other studies, the same range of gestational ages and mean birth weights were observed, but in contrast to our study, the males were more involved (16, 21-23). In some other studies, higher birth weights were observed (7, 20, 23). The mean of head circumference at birth, at discharge, and at 40 weeks was the same as mentioned by other studies (16, 24), but differs from measurements mentioned by others (26); the head circumference was smaller, as this study was done in extremely premature babies only, those with weights less than 1000 grams. Hospital stays for most premature babies were long, but to avoid the risk of complications like infection and parental separation, most centers tend to limit the duration of hospital stays. In our situation the bed capacity is one of our limitations in the duration of admission. In the study the majority stayed less than 3 weeks and maybe less, especially those with high gestational age or higher weight, as in some studies (7, 20); in contrast, there were premature babies who stayed for nearly 2 months in the unit; it was because of the development of complications like sepsis, apnea, or failure to gain weight (16, 22, 24, 25).

However, the most common morbidity in the study was respiratory distress syndrome (RDS), as in some studies (23, 24), and another was done in Korea by Lee et al. (25), which is a common risk facing premature babies in the NICU. Now it is becoming less common with the advancement of treatment like manufactured surfactant. Other morbidities have become more prevalent, like sepsis, which was mentioned as the first common morbidity in a study done by Liao et al. (21) and the second in other studies (24). In other studies, other morbidities were reported in large numbers, like hypothermia (20) and retinopathy of prematurity (ROP).

Extra-uterine growth restriction (EUGR) is defined as the growth measurement of weight, length, and

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head circumference below the 10th percentile of expected intrauterine growth at postmenstrual age (PMA) at discharge, 36 weeks, or 40 weeks corrected age. In our study we estimated the EUGR between the study group at discharge and 40 weeks corrected age. The results showed that EUGR was higher at discharge (79.4%) as compared to 40 weeks corrected age, which was 58.9%. This decreasing of EUGR at 40 weeks can be explained because most of the babies at this age were at home, as the premature baby stayed at home under the care of their parents, and with good social parental bonding, usually the chance to accept good weight before reaching 40 weeks is high. On the other hand, during the early days of admission, most premature babies, especially with lower birth weight and lower gestational age, had poor weight gain at discharge, which can be attributed to a lot of challenges they faced during admission, and that was reported in the study done in Spain as compared to studies conducted by others where 77% had EUGR at discharge, and it mentioned that it occurred in the first early period of admission (16). Either EUGR at discharge or at 40 weeks, the frequency is still high, and one of the important issues related to that is the delay in initiation of aggressive feeding, either enteral or parenteral, in most NICUs worldwide (7, 21-24). Some meta-analyses and studies found that EUGR was because the infants were receiving less protein and fewer calories (unaggressive feeding protocol) than that recommended by guidelines from international societies. Another cause is lack of breast milk fortification. Morbidities like BPD, IVH, NEC, and ROP (retinopathy of prematurity) represent other causes of EUGR. This can be overcome by increasing the calories up to 160 kcal/kg/day, protein to 4.5 g/kg/day, glucose up to 12.5 upto12.5g/kg/day, fat to 8 g/kg/day (14).

There were a lot of clinical characteristics that were significantly associated with risk of EUGR as compared to the non-EUGR group for discharge weight; they included birth weight, gestational age, weight for gestational age, duration of hospital stay, and multiple pregnancy. For weight at 40 weeks, birth weight, weight for gestational age, and duration of hospital stay were the factors significantly associated with EUGR, but multiple pregnancy and gestational age weren't. This is in line with a previous study done in Shanghai by Shan et al. that revealed the duration of hospital stay, birth weight, gestational age, and SGA are positively correlated to the development of EUGR in premature babies (7). Another study in Taiwan reported that especially extremely low birth weight had poorer growth outcomes (21). Lower birth weight, SGA, and lower gestational age were mentioned in a lot of studies as risk factors for EUGR (16, 20, 22, 24, 25). Because premature babies, especially those weighing less than 1500 grams, take longer to achieve full demand of feeding, that is why now faster aggressive feeding is recommended to get the target of optimal growth for premature babies for good neurodevelopmental outcome, not only for gaining weight. A study done by Burçin İşcan reported in his study that the EUGR group took longer to achieve total enteral nutrition than the Non-EUGR group (26). However, in our study, females were more frequent in the EUGR group, but the sex was negatively correlated with risk for EUGR both at discharge age and 40 weeks, which also was detected by a lot of studies done in other countries (20, 21, 24).

Regarding postnatal morbidities that occur due to a lot of complications that premature babies face in the NICU because of long hospital stays, which increase the risk of EUGR, sepsis was a significant risk factor for EUGR. actually that was one of the causes that lead to delay in initiation of feeding to premature particularly with extremely birth weight and very low birth weight and that increase the risk of EUGR in NICU, in the study was done by Lee et al 2799 infants was enrolled and conducted from 2013 to 2014 ,sepsis reported as positively correlated risk factor for EUGR in addition to respiratory distress syndrome and broncho-pulmonary dysplasia which both unlike in our study were not revealed significantly effected on EUGR(22) which are still common causes of admission and long stay of hospital for premature , sepsis demonstrated as

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significant factor for EUGR also in line with other researches were done in in china as prospective multi-center ,study in USA and in Turkey (23,24 ,26)

CONCLUSION

Extra-uterine growth restriction is one of the challenges facing the outcome of premature babies that survive, which is not a matter of weight gain but rather its relation to neurodevelopmental outcome for preterm babies who survive. It needs encouragement to start feeding, especially in critically ill infants, for whom a lot of research has proved that the benefits of early initiation of feeding outweigh the harm.

RECOMMENDATIONS

It needs more efforts to support optimal nutrition, rapid aggressive initiation of good nutrition, and avoidance of fear of increased feeding when needed for good neurodevelopmental outcomes. advice for updating the feeding protocol and implementing it in NICUs. With new evidence that enteral feeds have a strong role and are superior to parenteral nutrition, this will support premature nutrition and overcome the unavailability of the parenteral one. We need extended research for the outcome after updating and implementing the feeding protocol.

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Conflict of interest:

We declare that there was no conflict of interest or any financial or nonfinancial support.

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