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Nutritional Status and Serum IGF-1 Levels as Predictors of Preterm Morbidities

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ABSTRACT

Background: Insulin-like growth factor 1 (IGF-1) plays an important role in the complex association between nutrition, growth and maturation in extremely and very preterm infants. Nevertheless, in this population, research on associations between IGF-1 and nutrition is limited. The aim of this study was to assess the incidence of postnatal retinopathy of prematurity(ROP) of preterm infants ≤ 32 weeks' gestation in relation to their serum IGF-1 levels and nutritional intake. When the baby had attained feeding at 70ml/kg and four weeks later, IGF1 and anthropometric measures were obtained. **Patients and methods**: this prospective study included 55 premature neonates born at gestational age of ≤32 weeks' gestation, who had been examined for development of ROP and had their serum level of IGF1been checked. **Results**: There was statistically significant difference found between patients with and without ROP regarding the level of IGF1 (p-value <0.001). Neonates with ROP had statistically higher CRP and were smaller in size than non ROP group(p<0.001). **Conclusion:** in conclusion, we found that retinopathy of prematurity was significantly associated with low level of umbilical cord blood IGF-1 levels in preterm children, thus, IGF-1 is a potential biomarker for an increased risk of developing severe ROP. In addition, ROP was found to be significantly linked with maternal risk factors such as Urinary tract infection, anemia, preeclampsia and antenatal steroid.

Keywords: preterm infants, insulin-like growth factor, nutrient intake, ROP.

1. Introduction

In order to maximize the premature infant's growth and development, including proper retinal vascularization, early nutritional supplementation is essential (Connor *et al.,* 2007). The Insulin-like growth factor-1 (IGF-1) system is a crucial endocrine component that determines fetal growth. The glucose–insulin axis, which enables a quick response to dietary changes, mediates IGF-1-dependent growth. IGF-1 concentrations typically rise throughout mid–late gestation to support the accelerated growth that typically takes place in the third trimester in utero. Thus, low postnatal development and numerous other preterm morbidities are associated with its insufficiency in preterm infants (Murray *et al.,* 2013). The endogenous IGF-1 in the brain increases the brain's use of glucose during development (Cheng *et al.,* 2000). The majority of the data supporting IGF-1 regulation of newborn vascular expansion originates from research on vascular development in the eye. One important non-oxygen regulated factor in the formation of retinal neurovascular tissue is IGF-1. Vascular endothelial growth factor (VEGF) signaling was discovered to be compromised at IGF-1 levels of 10 ng/mL (Bang *et al.,* 2014). It is likely that a variety of factors, including as reduced food availability, insulin action, hypoxia, and inflammatory cytokines, are contributing to this decline in IGF-1 levels (Kuipers *et al.,* 2012).

Following the advent of new treatments like mechanical breathing and the use of surfactants, the number and survival rate of preterm newborns with low birth weight have also grown in neonatal

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intensive care units (NICUs), leading to an increase in morbidities. One of the most prevalent eye conditions in preterm babies is called ROP, which is defined by aberrant growth of retinal blood vessels. A number of perinatal-neonatal characteristics and maternal risk factors were assessed for their relationship to the development of ROP, which indicates the severity of the condition (Leonardi *et al.,* 2008; Dhaliwal *et al.,* 2009; Fierson 2013; Gagliardi *et al.,* 2013). Severe ROP can cause blindness and retinal detachment if left untreated (Blencowe *et al.,* 2010). ROP has reportedly been linked to blindness.

According to reports, ROP causes blindness in over 50,000 children globally each year (Zin and Gole*,* 2013). In order to prevent ROP-induced blindness, prompt treatment and appropriate screening are crucial (Moreira *et al.,* 2010).

Standardized feeding standards may lessen the variance in dietary practices, which can support growth in premature newborns, who are particularly susceptible to disorders connected to nutrition. The first stage in providing standardized nutrition recommendations is nutritional risk screening. However, there are few risk screening instruments designed specifically for monitoring preterm newborns. Although it is commonly used, body weight does not indicate the proportions of internal compartments. The mid-upper arm circumference is a simple way to quantify body adiposity. If measured precisely, body length indicates both fat-free mass and skeletal growth. Brain growth is indicated by head circumference. Skin folds are a reliable indicator of body fat.

Preterm neonates are more likely to experience nutrition shortages due to their fast growth rate, immaturity of many organs and systems, and challenges in supplying enough nutrition. ROP and other comorbidities including peri-intraventricular hemorrhage (PIVH), bronchopulmonary dysplasia (Bronchopulmonary dysplasia), and sepsis are frequently found in preterm newborns and are considered risk factors for morbidity and/or mortality. These conditions are in addition to growth deficit, inadequate nutrition, and high infection rates, all of which are linked to longer hospital stays (Alyson and Hassib 2021)

The aim of this study is to assess the relevance of postnatal nutritional status of preterm infants ≤ 32 weeks' gestation to their serum IGF-1 levels, and their possible correlation to preterm morbidities during neonatal period, including postnatal catch-up growth, the incidence and severity of ROP, and the development of IVH, Necrotising enterocolitis or Bronchopulmonary dysplasia.

2. Patients and Methods

2.1. Patients and study design

This prospective longitudinal (follow-up) study, included 55 premature neonates born at gestational age of ≤32 weeks' gestation, based on fetal U/S and postnatal clinical assessment of gestational age (modified Ballard score) (Ballard JL *et al.,* 1991), admitted to NICU and received feeding according to the routine protocol of feeding premature infants at the unit. Completion of the postnatal clinical follow-up period until the age corresponding to 36 weeks' gestation. The study was conducted from August 2021 to December 2022, at the NICU, Ain Shams University hospital. Neonates with occular congenital malformations or suspected chromosomal anomalies were excluded. Complete antenatal and perinatal history including gestational age, sex, twining, APGAR score, mode of delivery and premature rapture of membrane with a thorough clinical examination, cause of admission including small for gestional age, prematurity, PROM, sepsis, need of oxygen support. Maternal risk factors were recorded including Hypertension, diabetes mellitus, PROM, bleeding, urinary tract infection, anamia, preeclamsia and antenatal steroid.

2.2. Study tools

Gestational age was determined based on the first day of the last menstrual period and/or the first trimester ultrasound, and measured in completed weeks. Birth weight, length and head circumference within 24h postbirth were assessed to identify intrauterine growth status. Weight was measured placing the unclothed newborn on a digital SECA® scale with a measuring range of 0.1–15kg and an accuracy of ±5g; the length was determined by measurement of the crown-heel length and head circumference (occipitofrontal) with a flexible measuring tape accurate to 0.5cm. z-Scores of (birth) weight, length, or head circumference were calculated based on the Fenton 2013 growth chart (for preterm infants of corrected age before GA 40 weeks).

Involved neonates were clinically evaluated for postnatal catch-up growth regularly and two recordings were obtained for statistical analysis. Initial assessment by anthropometric measures was done upon attaining feeding of 70ml/kg, using Fenton 2013 charts, and the second was done 4 weeks later, altogether with IGF1serum levels evaluation.

Neonatal nutritional status was assessed by computing the total calorie intake (enteral or parenteral) during the study period and comparing the results between the first and second assessments. The daily macronutrient intake was computed using real intake information taken from medical records. The composition of the milk from one's own mother was determined using reference values, while the artificial milk was created by analyzing the given milk formula. Feeding of neonates was followed according to the international guidelines and the protocol of the NICU in Ain Shams University hospital [NICE Guideline (2020)].

ROP development and severity are assessed by ophthalmologists, and the incidence of ROP is correlated with IGF1 levels. After employing eye drops to dilate the pupillary distance, an indirect ophthalmoscope a specialized light device was used to view the retina. Scleral depression is a technique sometimes used to push the peripheral regions of the retina into view. An examination of a premature baby's retina is done to ascertain how far the retinal blood vessels have grown.

When a premature infant's retina is examined, it is possible to measure the zone the amount that the retinal blood vessels have grown and the stage the degree to which the veins are growing flat along the eye's wall. After the child's vessels reach zone III, it is often safe to remove them from additional ROP screening. The characteristics of the leading edge of developing retinal blood vessels (at the vascular-avascular border) are referred to as the stage of ROP. The International Classification for Retinopathy of Prematurity was used to categorize ROP (The International Classification of Retinopathy of Prematurity revisited, 2005).

Routine laboratory investigations were done according to the standard methods at the Central Laboratories of Ain Shams University Hospital, including complete blood count (CBC), C-reactive protein (CRP), electrolytes, liver function tests, kidney function tests, and coagulation profiles. From each participant, 3 mL of blood was taken by a sterile venipuncture under aseptic conditions into a serum separation vacutainer tube. Blood samples were clotted completely before serum separation by centrifugation at 3000 RPM for 20 minutes.

The neonates received feeding according to the unit protocols till the baby attained 70ml/kg at which, first IGF1 levels was evaluated, and another evaluation was done 4 weeks later.

Sera were used to assess levels of IGF1 by a commercially available human ELISA kit (BT Lab, Shanghai, China, cat. no. E0103Hu). The kit detection range is 0.1-40 ng/mL, and sensitivity is 0.058 ng/mL.

This study was approved by the Research Ethics Committee at the Faculty of Medicine, Ain Shams University, MS504/2021.

2.3. Statistical methodology

After data description and comparison, the change in IGF-1 over time was predicted for each individual using mixed models. The associations between nutrient intake, IGF-1, and potential confounders were assessed with regression analyses. The best cut-off point for IGF1 to detect cases with ROP was evaluated by receiver operating characteristic (ROC) curve analysis. All analyses were conducted using IBM® SPSS® Statistics 26 for Windows (IBM Corp., Armonk, NY, USA). Two-sided statistical significance was assumed at p-values less than 0.05.

3. Results

Table 1 : Demographic data of studied preterm neonates.

		No. = 53
Age (weeks)	Mean±SD	30.60 ± 0.93
	Range	28 – 32
Sex	Females	33 (62.3%)

	Males		20 (37.7%)
Twin	No		45 (84.9%)
	Yes		8 (15.1%)
APGAR at 10 min.	Median (IQR)		8 (7 – 8)
	Range		5 – 9
Mode of delivery	NVD		25 (47.2%)
	CS		28 (52.8%)

Table 2: Maternal risk factor of the studied preterm neonates

		ROP		Test value	P-value	Sig.
		Non-ROP No. = 25	**ROP No. = 28**			
Hypertension	Yes	8 (32.0%)	12 (42.9%)	0.663*	0.416	NS
Diabetes mellitus	Yes	8 (32.0%)	12 (42.9%)	0.663*	0.416	NS
PROM	Yes	17 (68.0%)	15 (53.6%)	1.149*	0.284	NS
Bleeding	Yes	17 (68.0%)	0 (0.0%)	28.031*	0	HS
Urinary tract infection	Yes	0 (0.0%)	4 (14.3%)	3.863*	0.049	S
Anemia	Yes	0 (0.0%)	6 (21.4%)	6.041*	0.014	S
Preeclampsia	Yes	0 (0.0%)	5 (17.9%)	4.929*	0.026	S
Antenatal steroid	Yes	19 (76.0%)	3 (10.7%)	23.186*	0	HS

P>0.05: Non significant (NS); P <0.05: Significant (S); P <0.01: Highly significant (HS)
•: Independent t-test; ≠: Mann-Whitney test; *: Chi-square test
ROP was more provenance among neonates of mothers with risk factors Urinary tract infection, anemia, preeclampsia and neonate's steroid.

Table 3: Caloric intake & respiratory support among the studied preterm neonates.

Expressed breast milk/formula	**Formula**	**26 (49.1%)**
	Milk	**27 (50.9%)**
Total caloric intake on evaluation(mean 5 days of age)	Median (IQR)	80 (70 – 128)
	Range	50 – 145
Total parentral nutrition(Total parental nutrition)	NPO	19 (35.8%)
	Partial	14 (26.4%)
	Total	20 (37.7%)
IV fluid	Median (IQR)	110 (95 – 155)
	Range	10 – 190
Type of respiratory support	Nasal CPAP	5 (9.4%)
	NPCPAP	6 (11.3%)

	NIPPV	8 (15.1%)
	SIMV	25 (47.2%)
	HFMV	9 (17.0%)
Surfactant	No	18 (34.0%)
	Yes	35 (66.0%)
Number of days on O2	Median (IQR)	20 (15 – 29)
	Range	8 – 38

Table 4 : Comparison between 1st evaluation and 2nd evaluation (4 weeks apart) regarding weight, OFC and length of the studied preterm neonates.

		1st evaluation	2nd evaluation	Test value•	P-value	Sig.
		No. = 53	No. = 53			
Weight (gm)	Mean±SD	1185.04 ± 110.21	1312.45 ± 150.10	-9.018	<0.001	HS
	Range	900 – 1400	1000 – 1590			
OFC (cm)	Mean±SD	30.94 ± 1.63	32.06 ± 1.57	-11.614	<0.001	HS
	Range	27 – 33	28 – 35			
Length (cm)	Mean±SD	41.74 ± 1.39	42.84 ± 1.33	-15.388	<0.001	HS
	Range	39 – 44	40 – 45			

OFC: occipitofrontal circumference
P>0.05: Non-significant (NS); P <0.05: Significant (S); P <0.01: Highly significant (HS)
•: Paired t-test

Table 5: Follow up for anthropometric measures of ROP group

ROP		1st evaluation	2nd evaluation	Test value	P-value	Sig.
		No. = 25	No. = 25			
Weight (gm) 1st evaluation	Mean±SD	1160.79 ± 97.29	1206.07 ± 99.12	-4.599	0.000	HS
	Range	980 - 1320	1000 - 1400			
OFC (cm) 1st evaluation	Mean±SD	31.21 ± 1.73	31.89 ± 1.66	-7.550	0.000	HS
	Range	27 - 33	28 - 34			
Length (cm) 1st evaluation	Mean±SD	41.86 ± 1.60	42.73 ± 1.57	-13.219	0.000	HS
	Range	39 - 44	40 - 45			

The previous table shows that there was statistically significant increase in the weight, OFC and length of the studied preterm neonates ROP at the 2nd evaluation than the 1st evaluation with p-value <0.001, <0.001 and <0.001; respectively.

Table 6: Relation of ROP with demographic data and anthropometric measures of the studied preterm neonates

		ROP		Test value	P-value	Sig.
		Non-ROP No. = 25	**ROP No. = 28**			
Age (weeks)	Mean±SD	30.56 ± 0.82	30.64 ± 1.03	-0.322•	0.749	NS
	Range	29 - 32	28 - 32			
Sex	Females	20 (80.0%)	13 (46.4%)	6.335*	0.012	S
	Males	5 (20.0%)	15 (53.6%)			
Twin	No	24 (96.0%)	21 (75.0%)	4.545*	0.033	S
	Yes	1 (4.0%)	7 (25.0%)			
APGAR at 10 min.	Mean±SD	9 (8 – 9)	7 (6 – 7.5)	6.078≠	0.000	HS
	Range	6 - 9	5 - 8			
Weight (gm) 1st evaluation	Mean±SD	1212.20 ± 119.22	1160.79 ± 97.29	1.727•	0.090	NS
	Range	900 - 1400	980 - 1320			
Weight (gm) 2nd evaluation	Mean±SD	1431.60 ± 98.86	1206.07 ± 99.12	8.279•	0.000	HS
	Range	1190 - 1590	1000 - 1400			
OFC (cm) 1st evaluation	Mean±SD	30.64 ± 1.50	31.21 ± 1.73	-1.285•	0.204	NS
	Range	28 - 33	27 - 33			
OFC (cm) 2nd evaluation	Mean±SD	32.24 ± 1.48	31.89 ± 1.66	0.799•	0.428	NS
	Range	30 - 35	28 - 34			
Length (cm) 1st evaluation	Mean±SD	41.60 ± 1.12	41.86 ± 1.60	-0.669•	0.506	NS
	Range	39 - 44	39 - 44			
Length (cm) 2nd evaluation	Mean±SD	42.96 ± 1.02	42.73 ± 1.57	0.618•	0.540	NS
	Range	41 - 45	40 - 45			

ROP was more prevalent among males, twin, preterm neonates with low APGAR score and low birth weight.

Table 7 : IGF-1 and CRP in non ROP and ROP cases at 1st evaluation and 2nd evaluation (4 weeks later)

		1st evaluation		2nd evaluation	
		Non-ROP	**ROP**	**Non-ROP**	**ROP**
		No. = 25	**No. = 28**	**No. = 25**	**No. = 28**
IGF1	Mean±SD	12.93 ± 0.82	8.37 ± 0.76	33.62 ± 3.40	15.86 ± 0.86
	Range	14-Nov	7 - 9.5	27 - 38	14 - 17
CRP	Mean±SD	4 (2 – 34)	14.8 (4.25 – 29.65)	6 (5 – 11)	11 (5 – 19)
	Range	1 - 60	2.1 - 67	3 - 40	2 - 50

Table 8 : Relation of ROP with other comorbidities, fluid intake, nutrition and caloric intake of the studied preterm neonates

			ROP		Test value	P-value	Sig.
			Non-ROP	**ROP**			
			No. = 25	**No. = 28**			
Mode of delivery		NVD	9 (36.0%)	16 (57.1%)	2.369*	0.124	NS
		CS	16 (64.0%)	12 (42.9%)			
Nutritional support	Expressed Breast	Artificial feeding	5 (20.0%)	21 (75.0%)	15.987*	0.000	HS
		Milk	20 (80.0%)	7 (25.0%)			
	Total caloric intake	Mean±SD	130 (120 – 140)	70 (65 – 77.5)	19.380≠	0.000	HS
		Range	100 - 145	50 - 85			
	Total parentral nutrition	NPO	0 (0.0%)	19 (67.9%)	40.102*	0.000	HS
		Partial	5 (20.0%)	9 (32.1%)			
		Total	20 (80.0%)	0 (0.0%)			
IV FLUID		Mean±SD	155 (140 – 171)	95 (90 – 100)	10.120≠	0.000	HS
		Range	100 - 190	10 - 120			
Respiratory support	Type of respiratory support	Nasal CPAP	3 (12.0%)	2 (7.1%)	10.368*	0.035	S
		NPCPAP	3 (12.0%)	3 (10.7%)			
		NIPPV	7 (28.0%)	1 (3.6%)			
		SIMV	11 (44.0%)	14 (50.0%)			
		HFMV	1 (4.0%)	8 (28.6%)			
	Number of days on O2	Mean±SD	20 (16 – 29)	19.5 (15 – 29)	0.345≠	0.732	NS
		Range	11 - 35	8 - 38			
	Surfactant	Yes	13 (52.0%)	22 (78.6%)	4.158*	0.041	S
HD		Yes	7 (28.0%)	17 (60.7%)	5.705*	0.017	S

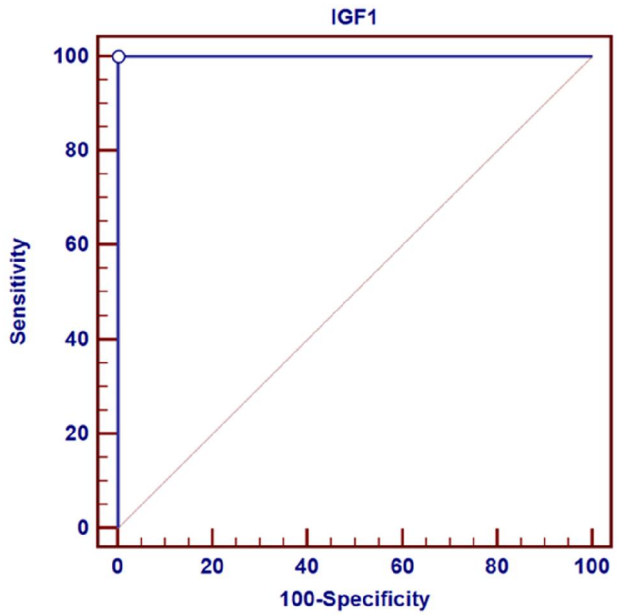
Intraventricular hemorrhage	Yes	4 (16.0%)	7 (25.0%)	0.650*	0.42	NS
Bronchopulmonary dysplasia	Yes	9 (36.0%)	11 (39.3%)	0.061*	0.805	NS
Necrotising enterocolitis	Yes	4 (16.0%)	2 (7.1%)	1.032*	0.31	NS
SEPSIS	Yes	9 (36.0%)	21 (75.0%)	8.178*	0.004	S
Blood Transfusion	Yes	6 (24.0%)	13 (46.4%)	2.889*	0.089	NS
PLT treatment	Yes	5 (20.0%)	20 (71.4%)	14.018*	0	HS

P>0.05: Non significant (NS); P <0.05: Significant (S); P <0.01: Highly significant (HS)
•: Independent t-test; ≠: Mann-Whitney test; *: Chi-square test

Table 9 : Univariate and multivariate logistic regression analysis for factors associated with ROP

	Univariate				**Multivariate**			
	P-value	**Odds ratio (OR)**	**95% C.I. for OR**		**P-value**	**Odds ratio (OR)**	**95% C.I. for OR**	
			Lower	**Upper**			**Lower**	**Upper**
Sex (male)	**0.015**	4.615	1.350	15.784	–	–	–	–
Twin	0.061	8.000	0.908	70.460	–	–	–	–
APGAR at 10 min. <=7	**0.000**	15.750	4.005	61.939	–	–	–	–
Antenatal steroid	**0.000**	0.038	0.008	0.171	–	–	–	–
Expressed Breast (Milk)	**0.000**	0.083	0.023	0.306	–	–	–	–
IV FLUID <=110	**0.000**	310.500	26.421	3649.050	**0.000**	310.500	26.421	3649.050
Type of respiratory support (NIPPV)	**0.034**	0.095	0.011	0.841	–	–	–	–
Surfactant	**0.046**	3.385	1.023	11.193	–	–	–	–
SEPSIS	**0.006**	5.333	1.635	17.402	–	–	–	–
PLT treatment	**0.000**	10.000	2.787	35.885	–	–	–	–
PTT at 1st evaluation >46	**0.006**	7.333	1.780	30.205	–	–	–	–

ROC curve for IGF1 at evaluation 1 to predict ROP



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
≤ 9.5	1.000	100.00	100.00	100.0	100.0

Fig. 1: ROC curve shows that the best cut off point for IGF1 to detect cases with ROP was found ≤ 9.5 with sensitivity of 100%, specificity of 100% and area under curve (AUC) of 100.

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Bleeding	**0.030**	0.141	0.024	0.826	0.132	0.132	0.010	1.833
Antenatal steroid	**0.031**	0.089	0.010	0.804	0.174	0.087	0.003	2.934
Total Total parentral nutrition	**0.034**	0.126	0.018	0.859	0.661	1.867	0.114	30.519
IGF1 at 1st evaluation <=13.4	**0.001**	49.200	4.876	496.476	**0.009**	61.940	2.850	1345.939

4. Discussion

In order to maximize the premature infant's growth and development, including proper retinal vascularization, early nutritional supplementation is essential (Connor *et al.,* 2007). The Insulin-like growth factor-1 (IGF-1) system is a crucial endocrine component that determines fetal growth. The glucose–insulin axis, which enables a quick response to dietary changes, mediates IGF-1-dependent growth. IGF-1 concentrations typically rise throughout mid–late gestation to support the accelerated growth that typically takes place in the third trimester in utero. Poor postnatal development and numerous other preterm morbidities are associated with its deficit in preterm newborns (Murray *et al.,* 2013).

Growth is stimulated by insulin-like growth factor 1 (IGF-1), which is also involved in the intricate relationship between early nutrition intake, development, and maturity. Insulin and diet are the main sources of IGF-1 stimulation in preterm newborns. It is yet unknown, nevertheless, how much different macronutrients affect IGF-1 levels at different stages of postnatal life (Yumani *et al.,* 2015).

However, a previous study found that in preterm infants, the positive association between IGF-1 and nutrient intake was only evident after 30 weeks of postmenstrual age (PMA). In our study, we evaluate the relevance of postnatal nutritional status of preterm infants less than 32 weeks gestation to their serum IGF1 levels and their potential correlation to preterm morbidities during neonatal period. This implies that nutrition may only have a little window of time to affect early postnatal growth (Dorum *et al.,* 2019). Additionally, Hansen-Pupp *et al.* discovered that dietary intake only affected IGF-1 levels starting at 32 weeks PMA, not at lower postmenstrual ages. It is possible that variables other than maturity will affect when IGF-1 levels begin to react to dietary intake (Hansen-Pupp *et al.* 2011).

One of the primary causes of blindness in children globally is ROP. As such, it is critical to remove babies who are very susceptible to ROP. Risk factors for the development of ROP include preterm, high oxygen concentration, sepsis, blood transfusion, intraventricular hemorrhage, and erythropoietin use (Bashinsky, 2017).

As regard Preterm data of the studied patients. Age was ranged from 28-32 weeks with a mean value of 30.60 ± 0.93 weeks. More than half of patients 33(62.3%) were females while 20(37.7%) were males. About 8 out of patients were twin (15.1%). More than half of patients were delivered by CS 28(52.8%). Similarly, in the study of Yumani *et al.* the mean age of their studied group was 29± 1.8 weeks. More than half of them (50.9%) were males (Yumani *et al.* 2020).

Regarding the maternal factor of the patients under investigation, the current study revealed that 20 of the patients had hypertension, 20 had diabetes mellitus, 32 had prostatic hyperplasia, 17 had bleeding, 4 had urinary tract infections, 6 had anemia, 5 had preeclampsia, and 22 had prenatal steroids. This is comparable to research by Delnord & Zeitlin and Engström *et al.* which found that preeclampsia, PROM, diabetes, obesity, and hypertension in mothers were risk factors for preterm and newborn morbidities [(Delnord & Zeitlin, 2019), (Engström *et al.,* 2005)].

Furthermore, Engström *et al.* verified that fourteen mothers of children had preterm rupture of the membranes (PROM, >24 h before birth), and seventeen mothers (17/76) had preeclampsia Engström *et al.* (2005). Most of the study group (56/76) had betamethasone administered as part of their prenatal care. Still, a few research projects carried out by Broekhuijsen *et al.* (2015) and Mengistu *et al.* (2021) showed that hypertension is not associated with composite adverse perinatal outcome [(Engström *et al.,* 2005), (Broekhuijsen *et al.*,2015), (Mengistu *et al.* 2021)]

In our study we assessed the anthropometric measure in the second evaluation as compared with the first, we found weight, OFC and length was highly significant with p value < 0.001, <0.001 and < 0.001 and there is significant increase in the level of IGF-1 with p value 0.000. In concordance with our result Yumani *et al.* found increased level of IGF1 and subsequently weight (Yumani *et al.* 2020).

In our study we found that the difference between birth and four weeks later as follow; IGF-1 level increased from (7-14 nmol /L) to (14-38 nmol/L) however the study of Yumani *et al.*, between birth and the second week of life, IGF-1 levels dropped from 4.8 nmol/L to 3.2 nmol/L (Yumani *et al.* 2020).

86.8% of the patients in our study had comorbid conditions; of these, more than half had ROP and Sepsis (56.6% and 52.8%, respectively), followed by congenital heart disease (45.35), bronchopulmonary dysplasia (37.7%), intraventricular hemorrhage (20.8%), and Necrotising enterocolitis (11.3%). Three different forms of co-morbidity were present in about one-third of the

patients. Additionally, the 2005 study by Engström *et al.* (2005) confirmed the incidence of Necrotising enterocolitis with percentages of ROP and intestinal perforation of 3% and 9%, respectively. Additionally, Yumani et al.'s 2020 study found that 5.7% of the cases had ROP and 25.18% of the cases they evaluated had intraventricular hemorrhage [(Engström *et al.* 2005) , (Yumani *et al.* 2020)].

The present study showed that ROP was more prevalent among males and twins (p-value = 0.012 and 0.033; respectively). Also, low APGAR score was associated with increased ROP with p-value <0.001. Neonates with ROP was found to have lower weight at 2nd evaluation than patient with non ROP (p-value <0.001). Although non-significant, neonates with ROP had the same age as non ROP. Whereas, Woo *et al.* (2013) showed no significant difference between case of ROP and control regarding age, sex and weight. Also, he reported no differences in the mode of delivery or Apgar scores between the 2 groups. Apgar scores at 5 minutes tended to be lower in the ROP group than controls, although the results did not show statistical significance (6.5 vs. 7.2, P = 0.054). However, in the study of Khalesi *et al.* significant statistical differences were seen regarding gestational age (29.3±3.1 weeks in the ROP group vs. 31.9±2.2 in control group) and Apgar score (6.55±1.7 in the ROP group vs. 7.06±2.3 in the control group) (Khalesi *et al.* 2015).

In our study, we confirmed that nutrition has positive effect on neonatal health, as regards the incidence of ROP, it was lower in neonates who received expressed breast milk, partial, total parentral nutrition and neonates who attained rapid full oral intake. Also, albumin as reflection of adequacy of nutritional support, it was postulated that high serum albumin was associated with increased incidence of ROP.

In our study, we found formula intake was associated with more percentage of ROP while breast milk was associated with lower incidence of ROP. Also, neonates with ROP had received lower total calories (70 vs 130 in non ROP) and this could be explained by required cessation of feeding due to associated morbidities like feeding intolerance, sever sepsis and bad general condition. Also, out of 53 recruited neonates 25(non ROP) had received total parentral nutrition (partial and total) vs 28 ROP who were (NPO and partial Total parentral nutrition).

The present study showed that the percentage of patients with sepsis, thrombocytopenia and surfactant treatment was found higher in patients with ROP than those without ROP p-value (0.004, <0.001, 0.007 and 0.041) respectively, while no statistical significant difference found between both groups regarding the other studied parameters.

Regarding oxygen support, our study showed that higher number of neonates received oxygen had ROP (28) VS non ROP (25). Similary, the study of Khalesi *et al.* reported that oxygen therapy and phototherapy were higher in the ROP group (Khalesi *et al.* 2015).

In present study, anemia was more prevalent among neonates with ROP although non-significant. Also, our results were in line with the study of Tandon *et al.* (2022) as they found that anemia was a significant risk factor (RF) for ROP development. A significant association was observed in other studies (Banerjee *et al.,* 2015).

In our study there was no statistically significant difference in adjusted mean hemoglobin levels between the ROP and non-ROP group during the first evaluation (p = 0.282).and there were no significant differences were observed at the second evaluation. However, in study of Pheng *et al.* (2020), revealed that there was a statistical significant difference in adjusted mean hemoglobin levels between the ROP and non-ROP group during the first week of life (p = 0.038) but he found no significant intergroup differences in second evaluation. This is in the line with the results of many findings indicated that lower hemoglobin in the first week of life was associated with ROP, but did not influence its severity (Lundgren *et al.,* 2018; Lundgren *et al.,* 2018).

The current study showed that statistical significant difference between mothers of neonates with ROP and without regarding antenatal maternal risk factors; bleeding, Urinary tract infection, anemia, preeclampsia and antenatal steroid with p-value <0.001, 0.049, 0.014, 0.026 and <0.001; respectively. Hypertension, Diabetes mellitus, Urinary tract infection, anemia, preeclamsia and antenatal steroid were more prevlant among mothers of neonates with ROP.

Our study showed that ROP was more prevelant among mothers with hypertension, Diabetes mellitus, Urinary tract infection, anamia and preclamcia.In contrary to our results, the study of Woo *et al.* (2013) reported that there no differences between the case of ROP and control groups in terms of maternal age, parity, pre-eclampsia and premature rupture of membrane rates, prevalence of clinical

and histologic chorioamnionitis , or rates of antenatal steroid, tocolytics, and antibiotics treatment. Also he reported, no significant differences between the two groups as regard neonatal characteristics and morbidities of infants with ROP and controls (RDS, Bronchopulmonary dysplasia, Intraventricular hemorrhage, Periventricular leukomalecia, Necrotising enterocolitis and Patent ductus arteriosus), clinical variables (positive airway pressure, mechanical ventilation) and major treatments such as blood transfusions, indomethacin and surfactant use (Woo *et al.* 2013). This could be explained by different sample size and different inclusion criteria between their study and ours.

Our study showed that ROP was more prevalent with neonates with thrombocytopenia (p value =0.000). In contrary to our result the study of Şahinoğlu Keşkek *et al.* showed that low platelet count was significant risk factors for developing ROP (Şahinoğlu Keşkek *et al.* 2020).

Also, Jensen *et al*., showed a relation between thrombocytopenia and the existence of ROP. Also, Choręziak *et al.* stated that a statistically significant difference was found in the occurrence of thrombocytopenia (p = 0.015), platelet counts before the diagnosis of ROP (p = 0.008) (Jensen *et al.* 2011), (Choręziak *et al.* 2022).

In the present study, although non-significant, neonates with ROP had higher CRP. Similarly, the study of Borțea *et al.* confirmed ROP severity were found to have a statistical significant positive correlation with umblical cord inflammation and higher CRP (Borțea *et al.* 2023).

In the study in our hand, there was statistical significant decrease in the IGF-1 in patient with ROP than those without.

In our study, mean IGF1 level during 1st evaluation (8-12) nmol/l and during 2nd evaluation was (15-33) nmol/l. It was noted that IGF1 improved in 2nd evaluation in both groups, although it was lower in ROP patients in both occasions. Also, IGF1 level was lower in neonates with comorbidities in 1st vist (10 vs 13) p value= 0.000, also during 2nd evaluation (22 vs 36) p value=0.000. Smillary to our study Hellstrom *et al.* found that low IGF1 level after preterm birth had been associated with poor post natal development and neonatal morbidities (Intraventricular hemorrhage, Bronchopulmonary dysplasia, Necrotising enterocolitis and ROP) (Hellstrom *et al.* 2003).

Our study found an association between lower postnatal serum IGF-1 levels and the subsequent development of ROP. Similarly to our study, many studies showed that low IGF1 levels were risk factor for development of ROP (Hellstrom *et al.,* 2013), (Perez-Munuzuri *et al.,* 2010), (Anne *et al.,* 2017) and (Graham *et al.,* 2021). However, other studies did not find an association between lower postnatal serum IGF-1 levels and the subsequent development of ROP or severe ROP in their studies (de Alba *et al.,* 2021), (Chan-Ling *et al.,* 2018), and (Nagano *et al.,* 2023).

Conclusion

In conclusion, we found that retinopathy of prematurity was significantly associated with low level of umbilical cord blood IGF-1 levels in preterm children, thus, IGF-1 is a potential biomarker for an increased risk of developing severe ROP. In addition, ROP was found to be significantly linked with maternal risk factors such as UTI, anemia, preeclampsia and antenatal steroid.

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