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Low Weight Gain as Risk Factor for Retinopathy of Prematurity in Preterm Infant

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ABSTRACT

Background: Low weight gain during the first month of life in preterm infants might be an important contributory factor for the occurrence of retinopathy of prematurity (ROP).

Objective: Our study aimed to determine the effect of low weight gain on the incidence of ROP in premature infants.

Patients and methods: This prospective, one-year cohort study was conducted in the Neonatology Department, in collaborate with the Ophthalmology Department in the Faculty of Medicine, Zagazig University. The study included 72 preterm neonates.

Results: Out of the 72 screened infants, (41.7%) cases had ROP, among whom (35.7%) had stage I, (24.5%) had stage II (39.8%) had aggressive ROP stage III zone II, 60% had a threshold and (33.3%) with plus disease. There were statistically significant relations between ROP development and weight loss ($p<0.001$), (OR, 4.5; 95% CI 0.37-54.15), prolonged duration of admission, ($p<0.005$), prolonged duration of oxygen therapy ($p<0.002$), respiratory distress syndrome (RDs), ($p<0.001$), pneumonia ($p<0.013$), bronchopulmonary dyspepsia (BPD) ($p<0.005$), sepsis ($p<0.001$), anemia ($p<0.001$), intraventricular hemorrhage (IVH) ($p<0.005$).

Conclusion: Our study results suggest that low weight gain or weight loss in the first month of life may predict pre threshold ROP that requires treatment. It can help identify babies with poor periods after birth who are most at risk, also O_2 therapy, and its duration, RDs, pneumonia, sepsis, BPD, anemia, and IVH were found to be the most significant risk factors for ROP development in premature babies.

Keywords: Postnatal Growth Restricted, Prematurity, Retinopathy of prematurity

INTRODUCTION

The optimal growth after birth is important not only for survival but also for improving the long term outcomes of preterm infants. Despite recent improvements in the neonatal care of preterm infants, postnatal growth restriction is still prevalent among preterm infants during their stay in NICU **(1).** A new study found that an improved neonatal nutritional supply after birth is associated with good growth during early postnatal life. So, an adequate supply of nutrients must be provided to achieve optimal weight gain and prevent growth restriction **(2).** Early improvement in weight gain is an important parameter of neonatal nutritional status, and low postnatal weight has been associated with the incidence of aggressive ROP **(3).** Small gestational age and low weight at birth are the most important factors for the development of ROP. Other factors associated with the present of ROP include RDs, sepsis, anemia, thrombocytopenia, poor weight gain, and the infant's overall health **(4).**

There is an estimated 15 million neonate born prematurely every year worldwide. Declines in infantile mortality and increased survival of premature infants contribute to increased incidence of ROP **(5).**

Retinopathy of prematurity is also called Terry's Syndrome **(6).** ROP disease affecting preterm infants is caused by abnormal growth of retinal blood vessels **(7).** When a baby is born preterm, the retinal blood vessels can grow abnormally, most ROP resolves spontaneously, but when ROP is severe, it can cause damage to the retina, and may cause blindness **(8).** Ophthalmoscope can describe the retinal findings at the connection between the avascular and vascularized retina as stages. **Stage I** It's a faint demarcation line, **Stage II** It's an elevated ridge, **Stage III** is extraretinal fibrovascular tissue, **Stage IV** is sub-total retinal detachment, and **Stage V** is total retinal detachment**(9).**

Treatment of ROP is depending on its severity; some of them have side effects of their own, **(7).** The laser therapy could be for advanced ROP, but needs general anesthesia, which may be risky for premature infants **(10).**

As regard medications, injection of anti-vascular, endothelial growth factor prevents overgrowth of retinal blood vessels as intravitreal injection of bevacizumab and ranibizumab **(11).**

The aim of the present study was to determine the effect of low weight gain on the incidence of ROP in premature infants.

PATIENTS AND METHODS:

This prospective one-year cohort study was conducted in NICU Pediatric Department, in Collaborate with of Ophthalmology Department in the Faculty of Medicine; Zagazig University. It included 72 preterm neonates.

Inclusion criteria; preterm infants with gestational age at birth between 27-36 weeks

Exclusion criteria; Full-term infant, and preterm infant whose relative refused to participate in the study.

All preterm infants were subjected to **details medical history** with a focus on **demographic data** [gender, mode of delivery; Caesarean section (CS), normal vaginal delivery (NVD), admission status: inborn /out

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born, duration of admission, gestational age assessment by Ballard], **Cause of admission:** RDs, intrauterine growth restriction **(**IUGR), early sepsis, jaundice, poor feeding, and hypoglycemia. **Complication:** Anemia, late sepsis, late jaundice, BPD and IVH. Clinical Risk Index: as respiratory support and its duration (mechanical ventilation, Nasal continuous positive airway pressure (CPAP) and Nasal prongs).

Neonatal full clinical examination: general and systemic.

Monitoring growth: for the body weight (gram) were measured daily for the first 6 weeks of life, length (cm) and head circumference (cm), were measured weekly for the first 6 weeks of life. The growth rate was expressed as g/kg/day.

Fundoscopy Examination:

Ophthalmologists experienced in ROP screening performed retinal examinations. The first fundus examination was within the 31st to 33$^{rd.}$ postmenstrual week. Excluded from the study were preterm babies without complete ROP screening outcomes and who died before ROP screening. All infants were followed weekly until ROP regressed, thereafter every 2 weeks until complete vasculature or additional treatment was given. Follow-up was done with binocular indirect ophthalmoscopy and digital colour fundus images.

Ethical approval:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee, and written consent was taken from parents of registered preterm before their subjection in these studies. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

SPSS for Windows, (20.0) was used to perform the statistical analysis of the data. Numerical data were presented in terms of its median, mean, standard deviation, and range. The absolute and relative frequencies of categorical variables were used to describe them. Independent t-test was used to compare between quantitative independent groups. Chi-square test (X^2) or Fisher's exact test was used to compare qualitative data. COR (crude odds ratio), and CI (confidence interval) were also used. P-value <0.05 was considered significant and <0.001 was considered highly significant.

RESULT

ROP screening, for a total of (72) infants of which, 41.7% had ROP, 35.7% stage I, 24.5% stage II, and 39.8% of cases developed aggressive ROP stage III zone II, 60% of them had threshold, 33.3% had plus disease and 46.7% of neonates with ROP were treated by intravitreal injection, 53.3% were not treated, 33.4% of them improved spontaneously and 20% died (Table **1).**

Table (1): Frequency of the ROP among the studied patients according to fundus examination and the fundoscopy finding of ROP according to the stage, zone, threshold, Plus disease and their outcome

Variable	N=72	(%)
Normal fundus	42	58.3%
ROP	30	41.7%
Variable	**N=30**	**(%)**
STAGE I	10 (14.9)	35.7%
• Stage I, zone I	2	8.6%
• Stage I, zone II	2	8.6%
• Aggressive ROP stage I, zone III	6	18.5%
STAGE II		
• Aggressive ROP stage II zone II	8 (10.2) %	24.5%
STAGE III		
• Aggressive ROP stage III zone II	12 (16.6) %	39.8%
Threshold:		
• Yes	18	60%
• No	12	40%
Plus disease:		
• Yes	10	33.3%
• No	20	66.7%
Treated (intravitreal injection)	14	46.7%
Not treated		
• Spontaneous Improvement 10 (33.3 %)	16	53.3%
• Died 6 (20%)		

The demographic data of the study cases are shown in table 2.

Table (2): Relation between ROP and demographic data of the studied patients

Variables	Total		ROP		P Value
	N=72	(%)	Yes N= 30 (%)	NO N= 42 (%)	
Gender:					**0.25**
▪ Male	32	44.4%	10 (33.3%)	22 (52.3%)	
▪ female	40	55.6%	20 (66.7%)	20 (47.7%)	
Site :					<0.001**
▪ Inborn	46	63.9%	28 (93.3%)	18 (42.8%)	
▪ Out born	26	36.1%	2 (6.7%)	24 (57.2%)	
Mode of delivery					
▪ NVD	24	33.3%	10 (33.3%)	14 (33.3%)	**0.11**
▪ CS	48	66.7%	20 (66.7%)	28 (66.7%)	
Gestational age					**0.797**
▪ Mean ± SD	32.5 ± 2.16		32.8 ± 1.5	32.3 ± 2.5	
▪ Median(range)	32 (27-36)		32 (31-36)	32 (27-36)	
Duration of admission					**0.03***
▪ Mean ± SD	23.6 ± 9.2		27.2 ± 9.1	21.1 ±8.5	
▪ Median (range)	23 (7-45)		28 (16-45)	22 (7-42)	
▪ > 2 Weeks	12	16.7%	0 (0%)	12 (71.4%)	**0.005****
▪ <2 Weeks	60	83.3%	30 (100%)	30 (28.6%)	

Quantitative data are represented as number (%), *: Statistically significant, **: Statistically highly significant

Table **(3)** shows that there was a significant difference between neonates with ROP and those without ROP regarding cause of admission. Where RDs II, III and IV increased the risk of ROP by 1.67, 11.67, and 15 folds respectively, as well as sepsis, poor feeding, hypoglycemia, IUGR increased risk by 1.46, 14.4, 14.4, and 1.46 folds respectively.

Table (3): Relation between ROP and Apgar score and cause of admission of the studied patients

Variable	Total		ROP		P value	COR (95% CI)
	N=72	(%)	Yes N= 30 (%)	NO N= 42 (%)		
Respiratory distress						
RDs II	32	44.4%	8 (26.6%)	24 (57.1%)	**0.5**	1.6 (0.2-9.2)
RDs III	20	27.8%	14 (46.6%)	6 (14.2%)	**0.001****	11.6 (1.9-70.1)
RDs IV	8	11.1%	6 (20.1%)	2 (4.9%)	**0.01***	15 (1.6-136.1)
Apnea	6	8.3%	0 (0%)	6 (14.2%)	**0.135**	0.09 (0.005-1.7)
Early sepsis	7	9.6%	4 (13.3%)	3 (9.5%)	**0.6**	1.46 (0.18-11.74)
Poor feeding	4	5.6%	4 (13.3%)	0 (0%)	**0.07**	14.4 (0.7-279)
IUGR	8	11.1%	4 (13.3%)	4 (9.5%)	**0.711**	1.46 (0.18-11.74)
Hypoglycemia	4	5.6%	4 (13.3%)	0 (0%)	**0.07**	14.4 (0.7-279)
Early jaundice	6	8.3%	0 (0%)	6 (14.2%)	**0.1**	0.09 (0.005-1.7)

Data are represented as number (%),*: Statistically significant, **: Statistically highly significant

In our study concerning anthropometric measurement of the study cases, table **(4)** shows that there was a significant difference between neonates with ROP and those without ROP regarding discharge birth weight, which was lower in those with ROP, while there was no significant difference in other anthropometric measurements. Regarding body weight follow up there was a significant difference between neonates with ROP and those without ROP, where weight loss increased risk by 4.5 folds while normal weight gain was protective.

Table (4): Relation between ROP and anthropometric measurement, during admission and during discharge of the studied patients

Variables	Total N=72(%)	ROP		P Value
		Yes N= 30 (%)	NO N= 42 (%)	
Body weight follow up Normal weight gain (≥15 g/day) Low weight gain (↓15 g/day) Weight loss	 32 (44.4%) 20 (27.8%) 20 (27.8%)	 0 (0%) 12 (40%) 18 (60%)	 32 (76.3%) 8 (19%) 2 (4.7%)	<0.001**
Birth weight (gm) Mean ± SD	1705 ± 404.3	1726.6 ± 369.9	1690.4±431.1	0.711
Discharge weight (gm) Mean ± SD	1967.9 ± 356.2	1748.3 ± 202.1	2124.2±360.5	<0.001**
Birth length (cm) Mean ± SD	41.2 ± 2.6	41.1 ± 2.08	41.4 ± 2.9	0.63
Discharge length(cm) Mean ± SD	43.1 ± 1.5	43.8 ± 2.2	43.1 ± 1.5	**0.51**
Birth head circumference (cm) Mean ± SD	29.75 ± 2.42	29.04± 1.94	30.23± 1.39	0.004
Discharge head circumference (cm) Mean ± SD	31.13 ±1.25	30.86±1.30	31.61±1.02	**0.45**

Quantitative data are represented as number (%), *: Statistically significant, **: Statistically highly significant

Table **(5)** shows that there was a significant difference between neonates with ROP and those without ROP regarding complications, where sepsis, late jaundice, anemia, pneumonia, BPD, IVH and increased risk by 15, 2.13, 10.86, 7.27 and folds respectively.

Table (5): Relation between ROP and complications among the studied patients

Variable	Total		ROP		P Value	COR (95% CI)
	N=72	(%)	Yes N= 30 (%)	NO N= 42 (%)		
Late sepsis	36	27.8%	24 (80%)	12 (28.5%)	<0.001**	15 (4.29 – 52.48)
Late jaundice	18	15%	10 (33.3%)	8 (19.1%)	0.168	2.13 (0.72 – 6.27)
Pneumonia	10	13.9%	8 (26.7%)	2 (4.8%)	0.013**	7.27 (1.42 – 37.29)
Anemia	20	25%	16 (53.4%)	4 (9.5%)	<0.001**	10.86 (3.09– 38.01)
BPD	6	8.3%	6 (20%)	0 (0%)	**0.005***	∞
IVH	6	8.3%	6 (20%)	0 (0%)	**0.005***	∞

Data are represented as number (%),*: Statistically significant, **: Statistically highly significant

Table **(6)** shows that there was a significant difference between neonates with ROP and those without regarding respiratory support and their duration, nasal CPAP, mechanical ventilation (MV) and duration more than 2 weeks. Nasal prongs, NCPAP and MV increased risk by 1.49, 2.5, 8.3 and 1.25 folds respectively.

Table (6): Relation between ROP with respiratory support and duration of oxygen therapy among the studied patients

Variable	Total		ROP		P value	COR (95% CI)
	N= 72	(%)	Yes N=30 (%)	No N=42 (%)		
Nasal prongs	56	77.8%	26 (86.7%)	30 (71.4%)	**0.05**	1.49 (0.14 -1.75)
NCPAP	38	52.8	20 (66.7%)	18 (42.9%)	**0.02***	2.5 (0.9-6.5)
MV	22	30.6	12 (40.0%)	10 (23.8%)	**0.01***	8.3 (1.5-44.6)
Duration: >2 weeks <2 weeks	 20 52	 27.8 72.2	 16 (53.3%) 14 (46.7%)	 6 (14.3%) 36 (85.7%)	 **0.002***	4.86 (1.7 -13.91)

Data are represented as number (%),*: Statistically significant

DISCUSSION

Incidence of ROP depends on several items such as race, geographical area, quality of NICUs and the survival rate of neonates. The incidence of ROP varies from one country to another and also from one institute to another in the identical country, owing to the variations in economic status, screening programs, and perinatal care level at different institutions[12].

The incidence of ROP in our study was (41.7%); thirty from 72 cases. Our results are in agreement with the results of **Quinn *et al.*** [13] who reported an incidence of ROP were 43.1%**.** On revising the Egyptian studies regarding ROP incidence, **Abdel-Aziz *et al.*** [14] in a prospective study of 216 screened neonates, (66) 30.6% developed ROP. **Bassiounya *et al.*** [15] reported, out of the 402 screened preterm babies, (237) 59% cases had ROP, which was comparable to that in developing countries, such as Saudi Arabia 38.6% [16]**,** Iran 45.0% [17]**,** India 19.28% [18]**.**

In the present study, among the ROP cases, it was found that 35.7% of the infants had stage I, 24.5% had stage II, 39.8% of them had developed aggressive ROP stage III zone II, 60% had threshold and 33.3% had plus disease. None of the infants had stage IV or V. The absence of stages IV and V indicates that more cases of earlier ROP stags were documented by early screening. These data were in consistence with **Gaber *et al.*** [19] who reported that 42.6% of neonates included in the study had stage III ROP, followed by stage II ROP 26.8%, aggressive ROP 13.4%, and stage I ROP 12%. Similarly **Bassiounya *et al.*** [15] who reported that 42.6% having stage I and 45.1% having stage II ROP. Finally, **Abdel-Aziz *et al.*** [14] reported an incidence of 40.9%, 53.0%, and 6.1% or both stages I, II, and III respectively.

The demographic data of cases with ROP and those without ROP showed that the normal cases included 22 males (52.3%) and 20 females (47.7%) females. Concerning the ROP cases, they included 10 males (33.3%) and 20 females (66.7%) with no significant difference between them. A similar study conducted by **Awad *et al.*** [20] showed that the normal cases included 36 males (46.2%) and 42 females (53.8%) while among ROP cases there was 13 male (59.1%) and 9 females (40.9%) with no statistically significant difference between the two groups.

Regarding the duration of admission more than 2 weeks, there was a significant difference between neonates with ROP and those without ROP. A resembling study by **Khorshidifar *et al.*** [21] found that there was a significant association between duration of NICU admission and the incidence of ROP. Other a similar study conducted by **Dani *et al.*** [10] found that there was a significant association between ROP incidence and longer duration of stay in hospital ($p<0.001$).

Regarding body weight follow-up, in our study, weight loss increased risk by 4.5 folds, while normal weight gain was protective. In a similar study conducted by **Šarić *et al.*** [22] neonates with severe ROP, had a significantly (296.5 ± 135.3; $p<0.001$) lower weight gain on a postnatal day 28 compared to neonates with mild or free ROP. **Ding *et al.*** [23] found that low weight gain (OR, 2.65 ; 95% CI, 1.49–4.72) ≤ 12 g/d vs. > 18 g/d; P = 0.001) were associated with ROP. **Anvekar *et al.*** [24] found that time to regain body weight was longer in preterm infants with type I ROP than controls, but did not reach statistical significance (median 9 vs 7 days, OR 1.08, 95% CI 1.00–1.17, p=0.059). **Subramanya *et al.*** [25] found that there was a significant difference in weight growth rate in the two groups ($P<0.05$).

Several studies have demonstrated that low weight is an indicator of the progression of ROP. However, studies have measured the pattern of weight gain (g/kg/day) during the first month of life, and have shown that the use of predictive models that include postnatal weight gain can significantly reduce the number of infants who need to be screened[26]**.**

We noted that duration in NICU admission, RDs, early sepsis, poor feeding, hypoglycemia, IUGR increased risk by 15, 1.46, 14.4, 14.4, and 1.46 folds respectively and were significant risk factors for severe ROP incidence, and regarding complications of prematurity, we found a significant relation between ROP incidences and late sepsis, anemia, pneumonia, BPD, IVH and increased risk by 15, 10.86, 7.27 and folds respectively, while late jaundice increased risk by 2.13 fold. These findings agree with previous studies conducted by **Alsammahi and Basheikh** [5], **Awad *et al.*** [20] and **Taha *et al.*** [27]**,** which have found that the association between ROP and complex medical conditions.

Huang *et al.* [28] found that the sepsis increased the incidence for the occurrence of ROP (OR=2.16; 95% CI: 1.65–2.82), early onset sepsis increased risk by 2.50 fold, and late onset sepsis increased risk by 1.37 fold. **Awad *et al.*** [20] found that there was a significant association between sepsis and ROP incidence ($p=0.004$). **Lundgren *et al.*** [29] found that during the first week postnatal, infants with progression ROP (28%) more frequently developed anemia (42.9% versus 8.0%, P = 0.003)**. Freitas *et al.*** [30] found that lung diseases increased the risk of ROP by 2.49 folds (95% CI: 1.35–4.59), and increased the risk of pre threshold ROP by 9.58 folds (95% CI: 1.27–72.04)**.**

We found that the occurrence of IVH increased the risk of development ROP ($p=0.005$). In a resembling study conducted by **Dani *et al.*** [10] they found that IVH increased the risk of ROP by 2.055 folds. while **Chang** [31] found that IVH was associated with severe ROP that required treatment.

In the present study, we found that the jaundice increased the risk for ROP by 2.13 fold. A resembling study conducted by **Gaber *et al.*** [19] found that jaundice increased the risk for the occurrence of ROP by 2.1 fold. (95% CI: 1.2–3.7).

We evaluated the risk of oxygen therapy and their duration for the development of ROP, we found that the MV, nasal CPAP, and oxygen therapy duration more than 2 weeks were significantly higher among patients with ROP. While there was no significant difference regarding nasal prongs, but nasal prongs, N CPAP, and MV increased risk by 1.49, 2.5, 8.3, and 4.86 folds respectively. Our results coincides with other studies, that have confirmed the relation between the development of ROP and the CPAP use [20] and mechanical ventilation [19,27].

CONCLUSION

Our study results suggest that low weight gain or weight loss in the first month of life may predict pre threshold ROP that is requiring treatment. It can help to identify infants with poor postnatal period who are at greatest risk, also O_2 therapy, and its duration, RDs, pneumonia, sepsis, BPD, anemia, IVH, were found to be the most significant risk factors for ROP development in premature babies.

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