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Effect of preterm infant weight gain in the first month of life and feeding type on the development of retinopathy of prematurity stages

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Purpose. *To assess the effect of preterm infant first-month weight gain (FMWG) and feeding type on the development of retinopathy of prematurity (ROP) stages.*

Material and Methods: *We retrospectively reviewed the medical records of 200 preterm infants (gestation age (GA), 24-36 weeks; birth weight (BW), 670-2500 g) who were under supervision during 2015-2018 and underwent ROP screening in due time. The fundus was assessed as per the 2021 International Classification of Retinopathy of Prematurity, third edition. Statistical analyses were performed using SPSS26.*

Results: *The preterm infant FMWG was positively correlated with the GA ($r = 0.36$, $p < 0.05$) and the BW ($r = 0.36$, $p < 0.05$), and negatively with the stages of ROP ($r = -0.38$, $p < 0.05$). The FMWG for infants without ROP was 36% larger ($p = 0.000$) than for those with ROP. At a FMWG exceeding 367.5 g/month, severe ROP requiring preventive treatment will likely not develop with a sensitivity of 60% and specificity of 78%. The preterm infant FMWG was positively correlated with the feeding type ($r = 0.36$, $p<0.05$). Formula-only feeding was more common in preterm infants without ROP than in those with ROP ($\chi^2=4.6$, $p=0.045$). The odds ratio (OR) of no ROP was 2.54 times higher (95% CI, 1.22-5.29) in formula-only fed preterm infants than in mixed-fed preterm infants.*

Conclusion: *The preterm infant FMWG was positively correlated with the GA ($r = 0.36$, $p <0.05$) and the BW ($r = 0.36$, $p < 0.05$), and negatively correlated with the stages of ROP ($r = -0.38$, $p <0.05$). The risk ratio of developing severe ROP requiring preventive treatment was 3.31 higher (95% CI, 1.66-6.58) for preterm infants with a FMWG < 367.5 g/month versus those with a FMWG > 367.5 g/month. The FMWG was positively correlated with the feeding type. The OR of no ROP was 2.54 times higher in formula-only fed preterm infants than in mixed-fed preterm infants.*

Key words:

retinopathy, premature infants, retinopathy of prematurity, postnatal weight gain, feeding type, risk factors, laser coagulation, screening, retina

Introduction

Retinopathy of prematurity (ROP) is still one of the most common causes of childhood blindness worldwide and thus remains a steadfast challenge to neonatal ophthalmologists.

Despite recent advances in the screening and treatment of the disease, the factors determining the risk for severe ROP require further research. In recent years there has been growing interest in studies on postnatal weight gain (PWG) and preterm infant feeding type as potentially significant predictors of prematurity. Numerous clinical observations have suggested that an insufficient weight gain (WG) in the first weeks of life may be an independent marker for increased risk for developing ROP, especially in severely preterm infants [1].

In a study by Binenbaum and colleagues [2, 3], multivariate logistic regression was applied retrospectively to data from infants born with BW less than 1501 g or GA of 30 weeks or less at a single Philadelphia hospital between January 1, 2004, and December 31, 2009. In the model, BW, GA, and daily WG rate were used repeatedly each week to predict risk of Early Treatment of Retinopathy of Prematurity type 1 or 2 ROP. The authors concluded that the BW-GA-weight gain CHOP ROP model demonstrated accurate ROP risk assessment.

Löfqvist and colleagues [4, 5] used the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm to retrospectively review the medical records of 79 preterm infants born at less than 32 weeks' GA at two Swedish hospitals between February 12, 2001, and April 11, 2002. In this study, the WINROP system accurately identified all infants who developed proliferative ROP. A retrospective review was performed on all premature infants born at an American hospital between October 21, 2005, and December 12, 2008, who qualified for ROP screening. Both ROP evaluations and weekly weight measurements from birth to postmenstrual week 36 for 318 infants were entered into a computer-based surveillance system, WINROP. This system signaled an alarm when the rate of weight gain decreased compared with control subjects. In a US cohort, the WINROP system had a sensitivity of 100% and identified infants early who developed severe ROP. In a retrospective study in Sweden [4, 5], the

WINROP system accurately identified all infants who developed proliferative ROP.

The first Postnatal Growth and Retinopathy of Prematurity Study (G-ROP-1) developed new screening criteria with 100% sensitivity for type 1 ROP and 30% reduction of infants requiring examinations in a retrospective development cohort of 7483 infants from 29 North American hospitals in 2006-2012. Infants meeting 1 or more of the following criteria undergo examinations: GA less than 28 weeks or BW less than 1051 g; WG less than 120 g during age 10 to 19 days, WG less than 180 g during age 20 to 29 days, or WG less than 170 g during age 30 to 39 days; or hydrocephalus [6, 7].

Studies emphasized the importance of a personalized nutrition approach and early nutrition support as a key component of the prevention of ROP, because it is on this that the PWG depends [8]. In this context, assessing the parameters of physiological growth and nutrition becomes a key component of a personalized approach to the prevention of retinal vascular pathology.

In our clinical practice, however, we have observed the development of severe ROP in infants with a GA > 30 weeks and a BW > 1500 g. Therefore, there is a need for Ukrainian studies based on the above-mentioned parameters.

The purpose of this study was to assess the effect of preterm infant WG in the first month of life and feeding type on the development of ROP stages.

Material and Methods

We retrospectively reviewed the medical records of 200 preterm infants with a GA of 24 to 36 weeks and a BW of 670 to 2500 g. These infants were under supervision at the Odesa Regional Pediatric Clinical Hospital and Odesa Municipal Pediatric Clinical Hospital No. 2 between 2015 and 2018.

The risk factors singled out were the (1) WG in the first month of life and (2) type of feeding the preterm infant, and the subsequent analysis was based on these factors.

All these infants underwent ROP screening in due time. The fundus was assessed as per the 2021 International Classification of Retinopathy of Prematurity, third edition [9]. The preterm infants were divided into four groups: group 1 of 97 infants with avascular retinal areas (without ROP); group 2 of 63 infants with spontaneously regressed ROP (stage 1 ROP, stage 2 ROP or type 2 pre-threshold ROP); group 3 of 26 infants that required treatment for ROP (type 1 pre-threshold ROP); and group 4 of 14 with aggressive ROP. Infants with stage 4 ROP, stage 5 ROP or a fatal disease were excluded from the study.

Feeding types included mixed feeding (a combination of breast and formula milk) and formula only feeding. Unfortunately, no infants were fed with breast milk only.

Indirect ophthalmoscopy was conducted using a binocular ophthalmoscope, 30 D-lens, eyelid speculum and scleral depressor after topical anesthetic (oxybuprocaine hydrochloride 0.4%) was instilled. A combination of eye drops, 0.5% tropicamidum and 0.2% irifrin, was used to achieve mydriasis. Statistical analyses were performed using SPSS26 (IBM Corpration, Armonk, NY).

Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test data for normality. Because the distribution of most parameters was not Gaussian, data are presented as median (interquartile range [IQR]). Mann-Whitney U test was used to compare independent samples. Spearman rank correlation was used to assess the relationships between numerical variables. The level of significance $p < 0.05$ was assumed. The Receiver Operating Characteristic (ROC) curve analysis was conducted to assess the diagnostic value of an input variable and included the calculation of the Area Under the Curve (AUC) and using the Youden index to determine the optimal cut-off point. Analysis of frequency characteristics was performed using the 2x2 contingency table for computing the chi-square score. Odds Ratio (OR) was used as a measure of the effect of a factor and defined as the ratio of the odds of an event occurring in the group affected by the risk to the odds of it occurring in the control group. The OR with a 95% confidence interval (CI) denotes the effect size with the control group divided by the experimental group. Risk ratio (RR) was determined in two groups, the group with a WG larger than the cut-off, and the group with a WG smaller than the cut-off.

Results

The WG in the first month of life of the preterm infant was positively correlated with the GA ($r = 0.36$, $p < 0.05$) and the BW ($r = 0.36$, $p < 0.05$), and negatively correlated with the stages of ROP ($r = -0.38$, $p < 0.05$). Therefore, the larger the GA and the BW, the larger was the WG in the first month of life. However, the WG in the first month of life was smaller in infants with severe ROP compared with infants in other groups.

We analyzed median WG in the first month of life in groups with various stages of ROP (Table 1).

The median WG in the first month of life (IQR) for group 1 (450 g ([340-590]) was 30% larger ($p = 0.000$) than for group 2 (315 g [210-475]), 50% larger ($p = 0.000$) than for group 3 (225 g) and 36% larger ($p = 0.003$) than for group 4. Since there was no significant difference in the WG in the first month of life among groups 2 to 4, these groups were united into the group 2-4 for determining the difference in the WG in the first month of life between infants without ROP and those with various stages of ROP (Table 2).

The median WG in the first month of life for group 1 was 36% larger ($p = 0.000$) than for group 2-4. Therefore, the WG in the first month of life in the preterm infant was found to have an effect on the completion of retinal maturation: the WG in the first month of life in preterm infants without ROP was larger than in those with ROP.

While analyzing the frequency of severe ROP cases that had received preventive treatment, we took into account the preterm infant WG in the first month of life. The

Table 1. Weight gain in the first month of life in groups of the study

Group	Number of preterm infants	Weight gain in grams, median (interquartile range)	p
1	97	450 (340-590)	p_{1-2}=0.000 p_{1-3}=0.000 p_{1-4}=0.003
2	63	315 (210-475)	p_{2-3}=0.1 p_{2-4}=0.5
3	26	225 (176-360)	p_{3-4}=0.4
4	14	287 (210-340)	

Note: p_{x-y}, significance of difference between groups

Table 2. Weight gain in the first month of life in the group of infants without retinopathy of prematurity versus the groups of infants with various stages of retinopathy of prematurity

Group	Number of preterm infants	Weight gain in grams, median (interquartile range)	p
1	97	450 (340-590)	$p_{1-(2-4)}$=0,000
2-4	103	290(200-420)	

Note: p_{x-y}, significance of difference between groups

ROC curve was used when building the discrimination model (Fig. 1).

The discriminating ability of the model was significant, with AUC 0.683 (95% CI, 0.598-0.767). The Youden index (J) was used to define the optimal cut-off point. The Youden Index was maximal (J = 0.331) at a cut-off of 367.5 g/month for the preterm infant WG in the first month of life. Therefore, at a threshold of 367.5 g/month for the preterm infant WG in the first month of life, the optimal balance between the sensitivity and specificity of this diagnostic model is achieved. At a WG in the first month of life exceeding 367.5 g/month, severe ROP requiring preventive treatment will likely not develop with a sensitivity of 60% and specificity of 78%.

Table 3 shows the numbers of infants with various stages of ROP who had preventive treatment versus infants who did not develop ROP or had spontaneously regressed ROP, for a WG in the first month of life > 367.5 g/month and for a WG in the first month of life < 367.5 g/month. Preventive treatment for severe ROP was performed in 9 preterm infants and not performed in 89 preterm infants with a WG in the first month of life > 367.5 g/month. Preventive treatment for severe ROP was performed in 31 preterm infants and not performed in 71 preterm infants with a WG in the first month of life < 367.5 g/month. There was a significant difference between these groups (χ^2 = 12.76, p = 0.004). This indicates that preterm infants with a WG in the first month of life < 367.5 g/month are more likely to develop severe ROP requiring preventive treatment.

The risk ratio (RR) of developing severe ROP requiring preventive treatment was 3.31 higher (95% CI, 1.66-6.58) for preterm infants with a WG in the first month of life < 367.5 g/month versus preterm infants with a WG in the first month of life > 367.5 g/month.

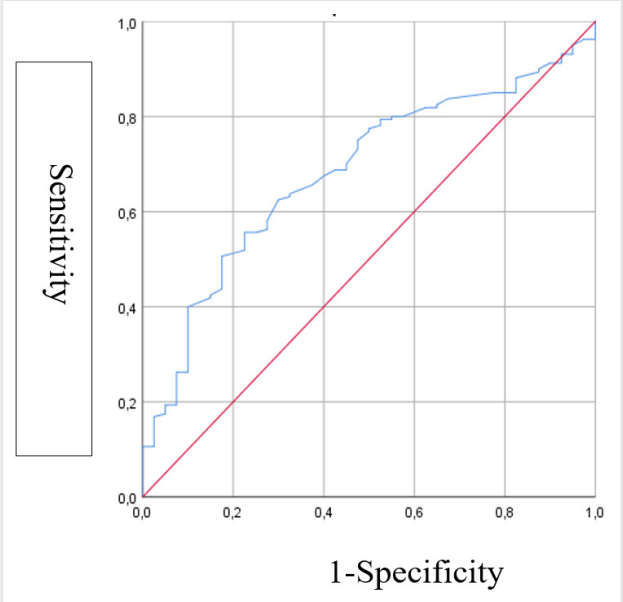

Fig. 1. Receiver Operating Characteristic (ROC) curve for the relationship between the preterm infant weight gain in the first month of life and the likelihood of developing severe retinopathy of prematurity

Additionally, the WG in the first month of life of the preterm infant was positively correlated with the feeding type (r = 0.36, p < 0.05). The WG in the first month of

Table 3. Numbers of infants that had a weight gain in the first month of life larger, versus smaller, 367.5 g, among preterm infants with various stages of retinopathy of prematurity who received, versus did not receive, preventive treatment of severe retinopathy

Preventive treatment of severe retinopathy of prematurity	Weight gain in the first month of life < 367.5 g	Weight gain in the first month of life > 367.5 g	p
	Number of preterm infants	Number of preterm infants	
Yes	31	9	0.004
No	71	89	

Note: p, significance of difference

Table 4. Numbers of infants that received formula feeding only versus mixed feeding among preterm infants without retinopathy of prematurity and infants with various stages of retinopathy of prematurity

Group	Type of feeding		p
	Formula feeding only	Mixed feeding	
	Number of preterm infants	Number of preterm infants	
1	26	71	p=0.045
2-4	13	90	

Note: p, significance of difference

Table 5. Numbers of infants that received formula feeding only versus mixed feeding among preterm infants in groups with various stages of retinopathy of prematurity

Group	Type of feeding		p
	Formula feeding only	Mixed feeding	
	Number of preterm infants	Number of preterm infants	
2	9	54	$p_{3-4} = 0.9$ $p_{2-4} = 0.9$ $p_{2-3} = 0.7$
3	3	23	
4	1	13	

Note: p, significance of difference

life of the preterm infant was larger in formula-only fed preterm infants than in mixed-fed preterm infants. In the current study, we analyzed the effect of the feeding type on the development of ROP (Table 4).

Moreover, we analyzed the effect of the feeding type on the development of ROP in infants with various stages of ROP (Table 5).

We found that formula-only feeding was more common in preterm infants without ROP than in those with various stages of ROP ($\chi^2 = 4.6$, $p = 0.045$). There was, however, no significant difference in the effect of the feeding type on the development of ROP among groups 2 to 4.

The odds ratio of no ROP was 2.54 times higher (95% CI, 1.22-5.29) in formula-only fed preterm infants than in mixed-fed preterm infants.

Formula-only feeding was used in 39 preterm infants, and mixed feeding, in 59 preterm infants with a WG in the first month of life > 367.5 g/month. Additionally, all preterm infants (102 preterm infants) with a WG in the first month of life < 367.5 g/month were mixed fed. There was a significant difference between these groups ($\chi^2 = 47.92$, $p = 0.000$).

Discussion

ROP is still one of the most common causes of childhood blindness worldwide. Despite significant advances in the treatment of ROP, the role of the WG in the first month of life and type of feeding in the pathogenesis is still actively studied and discussed. Leading studies in the developed countries have demonstrated the WG in the first weeks of life in preterm infants is not only a nutritional status characteristic, but also a sensitive biomarker of the risk of ROP. Monitoring this parameter enables non-invasive risk-based stratification of patients and optimization of screening algorithms. However, the infant

risk groups based on ROP screening criteria (like the GA and BW) in the developing countries are different from those in the developed countries, and the same is true for the WG in the first month of life [1].

The CHOP ROP study involved 524 infants born with BW less than 1501 g or GA of 30 weeks or less at a single Philadelphia hospital between January 1, 2004, and December 31, 2009. Multivariate logistic regression was applied for predicting the risk of type 1 ROP or type 2 ROP, and developing a BW, GA, and postnatal WG ROP prediction model in a cohort of infants meeting the screening guidelines. The model accurately predicted all infants with type 1 ROP and would have reduced the number of infants requiring examinations by 49% [2, 3].

G-ROP-1 was a retrospective study of 7483 infants from 29 hospitals, born between January 1, 2006, and December 31, 2011, who underwent ROP examinations and had a known ROP outcome, to develop postnatal WG-based modified ROP screening criteria. The study developed new screening criteria with 100% sensitivity for type 1 ROP and 30% reduction of infants requiring examinations. Infants meeting 1 or more of the following criteria undergo examinations: gestational age less than 28 weeks or birth weight less than 1051 g; weight gain less than 120 g during age 10 to 19 days, weight gain less than 180 g during age 20 to 29 days, or weight gain less than 170 g during age 30 to 39 days; or hydrocephalus. The prospective validation cohort study (G-ROP-2) was conducted at 41 hospitals in the United States and Canada from September 8, 2015, to June 13, 2017, among 3981 premature infants at risk for ROP and with known ROP outcomes. This study found that the G-ROP screening criteria were generalizable on validation. The G-ROP criteria had 100% sensitivity for predicting the infants who developed type 1 ROP in the development study cohort, while reducing by 30% the number of infants who would otherwise have received diagnostic retinal examinations [6, 7].

A 2006 study by Löfqvist and colleagues [4, 5] included 79 preterm infants born at less than 32 weeks' GA at the Queen Silvia Children's Hospital, Goteborg, Sweden, between December 18, 1999, and April 8, 2002, and at Uppsala University Hospital, Uppsala, Sweden, between February 12, 2001, and April 11, 2002. Body weight and serum IGF-I level measurements were performed weekly. The model correctly predicted 13 (100%) of 13 infants who developed ROP of stage 3 or higher. Therefore, an online surveillance system (the WINROP algorithm) was developed to evaluate the risk of severe ROP based on weekly postnatal measurements of serum IGF-1 levels and weight [4, 5].

A 2023 Indian prospective, observational study [10] aimed to study the relation between WG in infants and occurrence of ROP and was conducted on 62 premature infants. Mean gestational age and birth weight in treatable group (n = 26) were 31.38 weeks and 1572.31 g, respectively. ROC analysis revealed a cutoff of 29.33 g/day for ROP and 21.91 g/day for severe ROP requiring treatment. These cut-off values are lower than those in large multinational cohort studies [10].

The current study included infants with a GA of 24 to 36 weeks and a BW of 670 to 2500 g. We found that the larger the GA and the BW, the larger was the WG in the first month of life. The WG in the first month of life, however, was smaller in infants with severe ROP compared with infants in other groups . We also found that the median WG in the first month of life for the group of infants without ROP was 36% larger ($p = 0.000$) than for the groups of infants with various stages of ROP. While analyzing the frequency of severe ROP cases that had received preventive treatment, we found a threshold of 367.5 g/month for the preterm infant WG in the first month of life; this threshold should be given attention when screening preterm infants for ROP. That is, a preterm child with a 367.5-g WG in the first month of life will not develop a ROP stage requiring preventive treatment with sensitivity and specificity of 60% and 78%, respectively. This preterm infant WG in the first month of life is statistically significantly lower than that (450 g/month) found in the multicenter studies that were conducted in the developed countries. Moreover, we found that the risk ratio of developing severe ROP requiring preventive treatment was 3.31 higher (95% CI, 1.66-6.58) for preterm infants with a WG in the first month of life < 367.5 g/month versus preterm infants with a WG in the first month of life > 367.5 g/month. These findings are a valuable contribution to ROP screening and prognosis system.

Researchers give special attention to the type of feeding. Unprocessed breast milk contains nutrients and a variety of multifunctional bioactive factors involved in nutrient absorption, immune system maturation, antioxidant, and anti-inflammatory defense, gut microbiome establishment, food tolerability, and metabolism. However, energy and protein content is insufficient to stain growth in severely preterm infants, because breast milk content is modified in relation to maternal nutrition and infant characteristics such as BW, GA, stage of lactation, and sex, among others [11].

Zhou and colleagues' meta-analysis (2015) [12] included five observational studies. The meta-analysis concluded that based on current limited evidence, in very preterm newborns, human milk feeding potentially plays a protective role in preventing any-stage ROP and severe ROP. Furman and colleagues [13] and Heller and colleagues [14], however, concluded that, in extremely low birth weight infants, human milk intake was not associated with a decreased risk of severe ROP.

Current recommendations are based on a review by Hellström and colleagues (2024) [1]. Hellström and colleagues stressed that poor WG and low IGF-1 concentrations are strong risk factors for ROP. Neonatal enteral supplementation with arachidonic acid and docosahexaenoic acid, at levels similar to the fetal accretion rate, has been found to reduce severe ROP by 50% in randomized

controlled trials. The review emphasized the importance of a personalized nutrition approach and early nutrition support as a key component of the prevention of ROP [1].

The current study found that the WG in the first month of life of the preterm infant was positively correlated with the feeding type, with the WG in the first month of life of the preterm infant being larger in formula-only fed preterm infants than in mixed-fed preterm infants. Additionally, formula-only feeding was more common in preterm infants without ROP than in those with various stages of ROP ($\chi^2 = 4.6$, $p = 0.045$). There was, however, no significant difference in the effect of the feeding type on the development of ROP among groups 2 to 4. The odds ratio of no ROP was 2.54 times higher (95% CI, 1.22-5.29) in formula-only fed preterm infants than in mixed-fed preterm infants. We, however, need to continue the research on this risk factor and involve the breast fed only infants in the research.

Conclusion

First, the WG in the first month of life of the preterm infant was positively correlated with the GA ($r = 0.36$, $p < 0.05$) and the BW ($r = 0.36$, $p < 0.05$), and negatively correlated with the stages of ROP ($r = -0.38$, $p < 0.05$).

Second, the median WG in the first month of life for the group of preterm infants without ROP was 36% larger ($p = 0.000$) than for the group of preterm infants with various stages of ROP.

Third, the risk ratio of developing severe ROP requiring preventive treatment was 3.31 higher (95% CI, 1.66-6.58) for preterm infants with a WG in the first month of life < 367.5 g/month versus preterm infants with a WG in the first month of life > 367.5 g/month.

Finally, the WG in the first month of life of the preterm infant was positively correlated with the feeding type. Formula-only feeding was more common in preterm infants without ROP than in those with various stages of ROP ($\chi^2 = 4.6$, $p = 0.045$). The odds ratio of no ROP was 2.54 times higher (95% CI, 1.22-5.29) in formula-only fed preterm infants than in mixed-fed preterm infants.

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Disclosures

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Author's contribution. *All authors have the equal contribution to the paper.*

Ethical Declaration: ***T****his study involved human subjects, was approved by the local bioethics committee, and followed ethical standards as outlined in the Declaration of Helsinki. Informed consent was not obtained due to the retrospective nature of the study. This study did not include animal experiments.*

Conflict of interest: *All authors declare no conflict of interest that could influence their views on the subject matter or materials described and discussed in this manuscript.*

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Disclaimer. *The views expressed in this article are their own and not the official position of the institution.*

Data Availability Statement. *All the data obtained and analysed in this study has been reported in this study.*

Abbreviations: *AROP, aggressive retinopathy of prematurity; BW, body weight; GA, gestation age; ROP, retinopathy of prematurity; WG, weight gain; FMWG, first-month weight gain*