Research Article / Araştırma Makalesi

The Impact of Low Birth Weight and Gestational Age on Premature Retinopathy Outcomes

Düşük Doğum Ağırlığı ve Gebelik Yaşının Prematüre Retinopatisi Üzerindeki Etkisi

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Abstract

Background: The study aimed to investigate the incidence and treatment of retinopathy of prematurity (ROP) in premature infants, focusing on its relationship with gestational age and birth weight.
Materials and Methods: This retrospective study analyzed 1101 infants with a gestational age of 34 weeks or less and/or a birth weight of 1700 grams or less, screened for ROP between 2021 and 2023.
Results: Fifty-five infants required ROP treatment. ROP incidence was higher in lower birth weight and earlier gestational age groups. Among infants weighing 1000 grams or less, 56.1% developed ROP, compared to 43% in the 1001-1250 gram category and 28.1% in the 1251-1700 gram category. For gestational age, 53.2% of infants less than 27 weeks, 26.8% of 27-34 weeks, and 12.7% of over 34 weeks developed ROP.
Conclusions: Premature infants, especially those with very low birth weight and early gestational age, are at high risk for ROP, necessitating comprehensive screening and timely intervention.

Keywords: Retinopathy of prematurity, Birth weight, Gestational age, Laserphotocoagulation

Öz

Amaç: Çalışmanın amacı, prematüre bebeklerde prematüre retinopatisi (ROP) insidansı ve tedavisini araştırmak, özellikle gestasyonel yaş ve doğum ağırlığı ile ilişkisini incelemektir.
Materyal ve Metod: Bu retrospektif çalışma, 2021 ve 2023 yılları arasında ROP için taranan, gestasyon yaşı 34 hafta veya daha az ve/veya doğum ağırlığı 1700 gram veya daha az olan 1101 bebeği analiz etmiştir.
Bulgular: Elli beş bebek ROP tedavisi gerektirmiştir. ROP insidansı, daha düşük doğum ağırlığı ve daha erken gestasyonel yaş gruplarında daha yüksekti. 1000 gram veya daha az ağırlığındaki bebeklerin %56,1'i ROP geliştirirken, 1001-1250 gram kategorisinde %43 ve 1251-1700 gram kategorisinde %28,1 ROP geliştirmiştir. Gestasyonel yaşa göre, 27 haftadan küçük bebeklerin %53,2'si, 27-34 hafta arası bebeklerin %26,8'i ve 34 haftadan büyük bebeklerin %12,7'si ROP geliştirmiştir.
Sonuç: Prematüre bebekler, özellikle çok düşük doğum ağırlığı ve erken gestasyonel yaşa sahip olanlar, ROP için yüksek risk altındadır ve kapsamlı tarama ve zamanında müdahale gereklidir.

Anahtar Kelimeler: Prematüre retinopatisi, Doğum ağırlığı, Gebelik yaşı, Lazer fotokoagülasyon

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Introduction

Retinopathy of prematurity (ROP) is a retinal vascular disease characterized by the development of abnormal proliferation in the retinal vessels of premature infants (1,2). It was first noticed as a fibroblastic mass assembled behind the lens in premature infants. It was described as retrolental fibroplasia, referring to the pattern (3). Nowadays, it is understood that the pattern named retrolental fibroplasia in the past is Stage 5 ROP. In the 1940s and 1950s, the first ROP epidemic was experienced due to uncontrolled oxygen support and in the 1970s the second ROP epidemic was experienced due to the increase in the survival rate of very low gestational age infants as a result of medical and technological developments of the intensive care units (4,5). The frequency of retinopathy of prematurity varies according to the development levels of countries and the characteristics of neonatal intensive care units (6). In recent years, the increase in the incidence of ROP in developing countries draws attention. The most important factor in the pathogenesis of the disease is the continuation of retinal vascularization, which takes place in the relatively hypoxic intrauterine environment in the retina, under retinal hyperoxic conditions in a preterm infant (7). While the retina is avascular until the 16th week of pregnancy, the nasal retina at 36 weeks and the temporal retina at 40 weeks completes its vascularization. Therefore, in premature infants, the retina is not fully vascularized at the time of birth, and there is a peripheral avascular zone and its width varies according to the gestational age at birth (8). ROP is believed to develop through a two-stage process, although its exact pathogenesis is not fully understood. In premature infants, retinal vascularization, which begins in the intrauterine environment, is delayed by various damaging factors. These factors include prolonged hyperoxia, asphyxia, hypothermia, acidosis, and vitamin E deficiency, which are potential causes of the initial injury (9). In the early stage of ROP (phase 1), the suppression of vascular endothelial growth factor (VEGF) and erythropoietin due to hyperoxia, along with the absence of insulin-like growth factor 1 (IGF-1) and poor postnatal growth, hinders normal vascular development (10). Despite this, the retina continues to grow, leading to an unmet oxygen demand due to impaired retinal vascularization, resulting in retinal hypoxia and the onset of phase 2. During this phase, hypoxia triggers an increase in mediators such as VEGF, erythropoietin, and IGF-I, which leads to neovascularization.

Neovascularizations in the retina are observed at the vascular-avascular retinal border. First, neovascularizations cluster in the retina and form a rapidly thickening ridge tissue. If neovascularization progresses further, it may cause leakage and edema formation and retinal detachment leading to vision loss (11). In premature infants in phase-1, low IGF-1 levels in the early stages of life are usually due to prematurity itself and immature liver function rather than hypoxia. The immature liver function of premature infants leads to inadequate IGF-1 production, which negatively affects retinal vascular development. In phase-2, IGF-1 levels increase as the baby's nutrition improves and liver function improves. This increase works together with the release of VEGF caused by hypoxia to initiate the abnormal neovascularization process. While VEGF is expressed as the hypoxic retina's effort to form vessels, IGF-1 supports pathological vascular growth by increasing the effects of VEGF in this process. As a result, low levels of IGF-1 cause vascular development to lag behind, while the increase in IGF-1 and the interaction with VEGF contribute to the progression of ROP in the later period (9). These mechanisms are important in understanding the pathogenesis of the disease and determining therapeutic targets. Although our current knowledge is not sufficient to show in which infants the pathological process will occur, some risk factors have been reported in the light of clinical experience, revealing infants at risk (7). The best known risk factors are low birth weight and gestational age (10). In addition, many factors such as oxygen therapy, blood transfusion, acidosis, hypoxia, sepsis, and intraventricular bleeding have been thought to be associated with ROP (12).

Infants at risk of ROP should be screened and complications should be prevented by detecting and treating high-risk infants in a timely manner. Knowing the gestational ages and birth weights of the infants required treatment will shed light on who would be included in the screening. In this study, the rate of development and treatment of ROP in infants who were examined for ROP and the relationship of this rate with the gestational age and birth weight were examined. Appropriate screening criteria and methods for management of ROP were discussed.

Materials and Methods

Within the scope of the study, the records of 1101 infants with a birth age of 34 weeks and below and/or a birth weight of 1700 grams and below,and 34 weeks and above with a history of intensive care unit support who were examined for ROP between the years 2021-2023, were retrospectively analyzed. Before the examination, phenylephrine at 1.25% dilution and tropicamide at 0.5% dilution were dripped 3 times at 5 minutes intervals. Topical anesthesia with proparacaine hydrochloride was applied to infants with appropriate pupil dilatation. After the lids were opened with infant blepharosta, all retinal zones were examined with an indirect ophthalmoscope and +20 Diopter lens, with assistance of a scleral indentator. The subjects without retinopathy were followed up with 2-week intervals until peripheral retinal vascularization completed (approximately 45th gestational week). In cases with retinopathy, on the basis of the International PR Classification (ICROP-3) criteria[6], the severity of retinopathy between the vascular and avascular areas were described as (Stage 1 if there is a demarcation line, Stage 2 if there is a bulge or “ridge”, Stage 3 if extraretinal fibrovascular proliferation is detected, Stage 4a if there is partial retinal detachment not including the macula,Stage 4b if there is a partial retinal detachment including the macula, Stage 5

if total retinal detachment is present, Stage 5a if there is a total tractional retinal detachment but posteior pole is visualised with ophthalmoscopy,Stage 5b if there is closed funnel retinal detachment in the form of leukocoria, in which the retina is completely collected behind the lens,Stage 5c if there is a leukocoric tractional retinal detachment, in which the anterior chamber narrows and iridocorneal synechiae form, leading to corneal opacification over time). Follow-up periods of these patients were planned according to the current findings. The patients with high-risk according to the criteria of the ETROP (Early Treatment of Retinopathy of Premature) study group with pre-threshold disease signs (Plus disease with PR at any stage in Zone 1, stage 3 PR in Zone 1 without plus disease, Stage 2 or 3 PR in Zone 2 with plus disease) were underwent laser photocoagulation under general anesthesia. Surgical intervention via vitreoretinal procedures was implemented for cases presenting with retinal detachment. The cohort was stratified into distinct categories based on birth weight: ≤1000 g, 1001-1250 g, 1251-1700 g, a subtotal group (≤1700 g), 1701-2000 g, and ≥2001 g. Additionally, gestational age served as a criterion for further categorization: <27 weeks, 27-34 weeks, a subtotal group (≤34 weeks), and >34 weeks. All infants over 34 weeks or 1700 g had cardiopulmonary support treatment and considered high risk for developing ROP.These stratified groups underwent comprehensive analysis with respect to several parameters: the quantity of infants subjected to PR screening, the prevalence of PR (expressed as a percentage), the incidence of stage 3 and higher PR (percentage), the frequency of laser photocoagulation interventions (percentage), and the number of vitreoretinal surgical procedures performed. Furthermore, a comparative analysis was conducted between infants who were managed conservatively without intervention and those necessitating treatment. This analysis encompassed the number of patients in each group, their mean birth weight (including minimum and maximum values), and their average gestational age (with corresponding minimum and maximum values).

Statistics

Statistical analyses were conducted using SPSS for Windows, Version 29.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD). The Shapiro-Wilks test was employed to assess the normality of variables within a single group, confirming a normal distribution (p> 0.05). Consequently, the paired t-test was utilized to compare variables between pre-operative and post-operative periods. Pearson's correlation test was applied to examine the relationships between variables. A p-value of <0.05 was considered indicative of statistical significance.

Results

A total of 1101 infants were screened for retinopathy of prematurity. The mean gestational age of these infants was 30.5±2.530.5±2.5 weeks, ranging from 23 to 36 weeks. Their mean birth weight was 1516±435.61516±435.6 grams, with a range of 610 to 2850 grams. Among the screened population, 55 infants (5%) were diagnosed with retinopathy of prematurity at stages requiring therapeutic intervention. The mean birth weight of the infants who didn't need treatment was 1528.1±483 (550-2750) g, and the mean gestational age was 30.7±2.9 (23-37) weeks. The mean birth weight of the infants required treatment was 1152.2±396 (520-2120) g, the mean gestational age was 28.3±2.3 (24-34) weeks, and it was significantly lower than the patients who did not need treatment (p<0.001, Ki square test). Table 1 shows the comparison of infants followed up without treatment and infants requiring treatment according to mean gestational age and birth weight.

Table 1. Comparison of Mean Birth Weight and Gestational Age of Infants by Treatment Status

	Number of patients	Average birth weight (minimum-maximum)	Average gestational age (minimum-maximum)
Follow-up group	n=1046 (%95)	1548,6 g (610-2850)	30,6 weeks(23-36)
Treatment group	n=55 (%5)	1142,4 g (610-2225)	27,4 weeks (23-34)
Total	n=1101	1516 g (610-2850)	30,5 weeks (23-36)

g: gram. (Chi square test, p<0,001)

Considering the groups according to their birth weights, 66 (56.1%) of 123 infants born at 1000 g and below, 118 (8%) of 273 infants born between 1001-1250 g, and 86 of 305 infants born between 1251-1700 g (PR developed in 28.1%, 42 (12.9%) of 325 infants born between 1701-2000 g, and 1 (1.3%) of 75 infants born in 2001 g and above. The frequency of ROP by birth weight and the comparison of treated patients are shown in Table 2. PR development rate was found to be significantly higher in premature infants with low birth weight (p<0.001, chi-square test).

Considering the groups according to gestational age, 114 (53.2%) of 214 infants born below 27 weeks of age, 164 (26.8%) of 612 infants born between 27-34 weeks, and 35 of 275 infants born above 34 weeks (53.2%) 12.7) developed PR was detected. The frequency of PR according to gestational age and the comparison of treated patients are shown in Table 3. PR development rate was found to be significantly higher in infants born earlier (p<0.001, chi-square test).

It was determined that requirement of treatment decreased significantly as the birth weight of the patients increased. When examined according to the gestational age, it has been detected that the indication for treatment decreases with the increase in the birth week.

Table 2. Incidence of Retinopathy of Prematurity and Treatment Interventions by Gestational Age

Gestation age (grams)	Infants scanned for ROP	Infants with ROP (%)	Percentage of Stage 3 ROP and above (%)	Percentage of laser treatment(%)	Vitreoretinal surgery numbers
≤1000	123	66 (%56,1)	23 (%18,6)	25 (%20,3)	3
1001-1250	273	118 (%43,2)	15 (%5,5)	13 (%4,7)	1
1251-1700	305	86 (%28,1)	7 (%2,3)	8 (%2,6)	1
Subtotal (≤1700)	701	270 (%38,5)	45 (%6,4)	46 (%6,5)	5
1701-2000	325	42 (%12,9)	2 (%0,6)	3 (%0,9)	1
≥2001	75	1 (%1,3)	1 (%1,3)	-	-
Total	1101	313 (%28,4)	48 (%4,4)	49 (%4,5)	6

ROP; retinopathy of prematurity

Table 3. Prevalence and Severity of Retinopathy of Prematurity Stratified by Gestational Age: Screening Outcomes and Interventions

Gestation age (grams)	Infants scanned for ROP	Infants with ROP (%)	Percentage of Stage 3 ROP and above (%)	Percentage of laser treatment(%)	Vitreoretinal surgery numbers
<27	214	114 (%53,2)	32 (%15,0)	32 (%14,9)	4
27-34	612	164 (%26,8)	14 (%2,3)	16 (%2,6)	2
Subtotal (≤34)	826	278 (%33,7)	46 (%5,6)	48 (%5,8)	6
>34 weeks	275	35 (%12,7)	2 (%0,7)	1 (%0,4)	-
Total	1101	313 (%28,4)	48 (%4,4)	49 (%4,5)	6

ROP; retinopathy of prematurity

Discussion

Retinopathy of prematurity is an increasing, significant global issue of our time. Although significant advances have come out in the treatment of PR with cryotherapy and laser photocoagulation after the 1980s, 10-15% of the cases that undergone treatment continued suffering lose of vision (13). Technological and medical advances in treatment have led to a decrease in premature mortality and an increase in morbidity. In addition, inadequate care conditions and lack of a good screening program contribute to morbidity. The increased prevalence of multiple pregnancies due to the widespread use of assisted reproductive technologies, along with the associated rise in premature birth rates, also contributes to the incidence of ROP (14, 15). Nowadays, issues related to the diagnosis and follow-up of PR have become more prominent in recent years.

Since retinopathy of prematurity is a disease that can be completely or partially treated or its progression can be prevented when diagnosed early, premature infants should be examined by establishing a good screening program in terms of the first signs of ROP (16). The American Academy of Pediatrics recommends screening for ROP in infants born with a body weight of 1500 grams or less than 30 weeks, infants"at-risk"over 30 weeks of age (eg, those who have received long-term oxygen therapy), or infants at risk between 1500-2000 grams with accompanying systemic disease (17). It is recommended to screen infants with a gestational age of 31 weeks and below in Sweden, and infants with a gestational age of 32 weeks and below or with a birth weight of less than 1500 g in England (18). It has been emphasized that these criterias in developed countries will not be very suitable for countries with a lower socioeconomic development level and that the screening limit for these infants should be kept wider and should be decided according to local population characteristics (19).

The recommendations in the consensus guide of the Turkish Neonatology Association and the Turkish Ophthalmology Association are similar. It is recommended to screen all infants with a gestational age of 34 weeks and below or with a birth weight of 1700 g and older infants with cardiopulmonary issues and high risk for ROP (20). There are various studies on this subject in our country. Mutlu et al. stated that none of the infants over 32 weeks of age needed treatment in their studies (21). Yellow Kabadayi et al. similarly reported that it would be appropriate to screen infants born under 32 weeks and 1500 grams (22). On the contrary, in studies conducted by Özbek, stage 3 and more advanced PR findings were reported in a significant number of patients born above 1500 g and 32 weeks (23). In our study, our screening criteria were similar to the recommendations in the consensus guidelines of the Turkish Society of Neonatology and the Turkish Society of Ophthalmology. On the contrary, in our study, ROP developed in 42 (12.9%) of 325 infants born over 1700 grams and in 35 (12.7%) of 275 infants born over 34 weeks. These values were apart from the scope of screening according to the USA and UK criteria. So it is inevitable to establish a specific appropriate ROP screening guideline for every different population.

In our clinic, PR screening examination is performed with binocular indirect ophthalmoscopy and patients are examined in detail. Retcam™ (Clarity Medical Systems), a camera system that can take wide-angle digital images of the retina,

and phoenix ICON (trademark of phoenix ICON) have been put into use in some clinics abroad and in our country. Since these devices allow us to record photos, they offer the possibility of archiving images. It provides us an advantage due to its ease of application and a disadvantage of its low sensitivity. However, indirect ophthalmoscopy is the gold standard method for PR screening nowadays.

The best known risk factors for the development of retinopathy of prematurity are low DA and GA. It is known that the frequency of retinopathy increases significantly especially in infants born below 1000 grams and before 28 weeks (6, 10). In a multicenter study conducted in the United States between 2000 and 2002, the frequency of PR was 68% and the frequency of severe PR was found to be 36% in preterm infants born with a birth weight of less than 1251 g, while in another study these rates were found to be 68% and 12.4%, respectively (24,25). Our study found that as birth weight increased, there was a corresponding rise in the incidence of retinopathy of prematurity, the number of infants diagnosed with Stage 3 or higher PR, and the frequency of both laser photocoagulation and vitreoretinal surgeries. There are many studies on the effect of gestational week on PR. Selim Sancak et al. found the frequency of PR as 43.5% in a 4-year period in preterm newborns with ≤ 32 weeks of gestation (25).

Neonatal care should prioritize enhanced screening for infants at high risk of severe ROP, particularly those with very low birth weight and early gestational age. This includes frequent eye examinations to facilitate early detection. Timely intervention is crucial, necessitating standardized protocols for laser treatment and ensuring neonatal units are well-equipped and staffed. Educating parents about ROP and its management is vital, as is supporting ongoing research into alternative treatments. These strategies aim to improve outcomes for vulnerable infants, highlighting the importance of vigilant care and timely intervention in neonatal practice.

Study limitations

The potential risk factors for (ROP), such as oxygen therapy, total intubation period of the premature infants, blood transfusions, acidosis, hypoxia, sepsis and intraventricular bleeding weren't analized in the study.The infants underwent anti VEGF injections were a minority of the total premature infants, so they were excluded.Additionaly, the long term results of patients underwent pars plana vitrectomy (PPV) is unknown.

Conclusion

Findings of this study draws attention to the significance of PR screening and treatment. Due to the high comorbidity of retinopathy of prematurity, it is very important that premature births with risk factors are carefully examined and infants require treatment are treated promptly. A regular screening program should be prepared by the ophthalmologist and neonatologist together. When patients are discharged from the intensive care unit, families should be informed about the examination, and the continuity of follow-up and treatment should be the joint responsibility of the ophthalmologist, pediatrician and family. Informing the families regarding the severity of the disease may cause blindness, obtaining their consent before the examination, recording the control examinations by making an appointment through the system, and recording the examination findings both in the patient files and in the computer system will minimize the legal processes that may occur.

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