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Development of Retinopathy of Prematurity in Late Preterm Infants: Singleton or Multiple Pregnancies: Observational and Descriptive Research

Geç Preterm Bebeklerde Prematüre Retinopatisi Gelişimi: Tekil veya Çoğul Gebelikler: Gözlemsel ve Tanımlayıcı Araştırma

Eşay KIRAN YENİCE[a], Caner KARA[b]

[a]Department of Ophthalmology, University of Health Sciences Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital, Ankara, Türkiye
[b]Clinic of Ophthalmology, Ankara City Hospital, Ankara, Türkiye

ABSTRACT Objective: To investigate the role of singleton or multiple pregnancies in the development of retinopathy of prematurity (ROP) in late preterm infants. **Material and Methods:** The findings of preterm infants born at 32-35 weeks of gestation and without any perinatal risk factors were retrospectively evaluated. The relationship between risk factors and development of ROP was analyzed using logistic regression analysis. **Results:** Of the 2,364 preterm infants, 1,160 (49.07%) were singleton pregnancies and 1,204 (50.93%) were multiple pregnancies. ROP was detected in 3.13% (n=74) of the infants; 0.85% (n=20) of these were singleton pregnancies and 2.28% (n=54) were multiple pregnancies. ROP development was significantly higher in infants with a multiple pregnancy history (p=0.000), and gestational age (GA) and birth weight (BW) were significantly lower (p=0.000, p=0.003). While there was no significant relationship between gender and the development of ROP in univariate analysis, GA, BW, postmenstruel age at examination and multiple pregnancy were significantly associated with ROP (β=0.436, p=0.000; β=0.998, p=0.000; β=0.637, p=0.000; β=2.677, p=0.000, respectively). In multivariable analysis, GA (β=0.554, p=0.000), BW (β=0.999, p=0.001) and multiple pregnancy (β=2.375, p=0.001) were significantly associated with the development of ROP. **Conclusion:** In conclusion, this study supports that multiple pregnancies may cause preterm birth and low BW in late preterm infants and may play a role in the development of ROP. Therefore, it may be appropriate to examine late preterm infants for ROP at least once, especially in developing countries.

Keywords: Retinopathy of prematurity; singleton pregnancy; multiple pregnancy; late preterm infant

ÖZET Amaç: Geç prematüre bebeklerde prematüre retinopatisi (PR) gelişiminde tekil veya çoğul gebeliklerin rolünün araştırılması. **Gereç ve Yöntemler:** PR nedeniyle takip edilen, 32-35. gebelik haftaları arasında doğan ve herhangi bir perinatal risk faktörü olmayan yenidoğanların muayene bulguları geriye dönük değerlendirildi. PR gelişimi ile risk faktörleri arasındaki ilişki lojistik regresyon analizi kullanılarak analiz edildi. **Bulgular:** Çalışmaya dâhil edilen 2.364 yenidoğanın 1.160'ında (%49,07) tekil gebelik, 1.204'ünde (%50,93) çoğul gebelik öyküsü mevcuttu. Yenidoğanların %3,13'ünde (n=74) PR tespit edilmiş olup %0,85'inde (n=20) tekil gebelik, %2,28'inde (n=54) çoğul gebelik saptandı. Çoğul gebelik öyküsü olan bebeklerde tekil gebelik öyküsü olanlara göre PR gelişimi anlamlı olarak daha yüksek (p=0,000), gebelik yaşı (GY) ve doğum ağırlığı (DA) anlamlı olarak daha düşük idi (p=0,000, p=0,003). Tek değişkenli regresyon analizinde cinsiyet ile PR gelişimi arasında anlamlı bir ilişki bulunmazken, GY, DA, postmenstrüel muayene yaşı ve çoğul gebelik PR ile anlamlı düzeyde ilişkiliydi (sırasıyla β=0,436, p=0,000; β=0,998, p=0,000; β=0,637, p=0,000; β=2,677, p=0,000). Çok değişkenli regresyon analizinde ise GY (β=0,554, p=0,000), DA (β=0,999, p=0,001) ve çoğul gebelik (β=2,375, p=0,001) ile PR gelişimi arasındaki anlamlı ilişkinin devam ettiği gözlendi. **Sonuç:** Sonuç olarak, bu çalışma çoğul gebeliklerin geç preterm bebeklerde erken doğuma ve düşük doğum ağırlığına neden olabileceğini ve PR gelişiminde rol oynayabileceğini desteklemektedir. Bu nedenle özellikle gelişmekte olan ülkelerde geç prematüre bebeklerin en az bir kez PR açısından taranması uygun olabilir.

Anahtar Kelimeler: Prematüre retinopatisi; tekil gebelik; çoğul gebelik; geç preterm yenidoğan

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Correspondence: Eşay KIRAN YENİCE
Department of Ophthalmology, University of Health Sciences Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital, Ankara, Türkiye
E-mail: esay_kiran@hotmail.com

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Retinopathy of prematurity (ROP), one of the leading causes of preventable blindness in childhood, is a vasoproliferative disease of the immature retina.[1] While ROP in developed countries is limited to preterm and low birth weight (BW) infants, recent research has shown that more mature infants in developing countries may develop ROP due to exposure to risk factors.[2-5] The increase in the number of surviving premature infants along with the improvement of neonatal care brings with it an increase in the number of infants at risk of ROP.[6] Although best-known risk factors include early gestational age (GA) and low BW, the development of ROP is multifactorial. Potential risk factors include gender, mode of delivery, maternal age, multiple pregnancies, duration of oxygen supplementation, mechanical ventilation, blood transfusion, anemia, apnea and sepsis.[2,7-11] On the other hand, multiple pregnancies may increase the risk of preterm birth, resulting in low GA and low BW. Therefore, an increase in the number of infants with ROP can be observed. However, conflicting findings are reported regarding the effect of multiple pregnancies on ROP. A recent study stated that ROP is significantly more common in singleton pregnancies than in multiple pregnancies.[12] However, there are also studies reporting that multiple pregnancies are not a risk factor and that the incidence of ROP is similar in singleton and multiple pregnancies.[11,13,14]

Therefore, in our study, we aimed to investigate the role of singleton or multiple pregnancies in the development of ROP in late preterm infants.

MATERIAL AND METHODS

STUDY DESIGN

Preterm infants born at 32-35 weeks of gestation from 2010 to 2022 and without any perinatal risk factors were retrospectively examined. This study was approved by Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital Ethical Review Committee (date: January 30, 2023, no: 2023/01), conducted in line with the standards of the Declaration of Helsinki. Informed consent was obtained from all parents. Neonates born at <32 weeks and >35 weeks of gestation, with a history of eye surgery, trauma or severe eye diseases, and with inadequate data were not included in the study. We recorded the following information about the infants: gender, GA, BW, postmenstruel age (PMA) at examination, singleton or multiple pregnancies and ROP Stages and Zones. Infants were divided into two groups: singleton pregnancies (Group 1) and multiple pregnancies (Group 2).

ROP SCREENING

Infants were screened for ROP after pupil dilation at the 4th-6th weeks after birth. One hour before the examination, 0.5% tropicamide (Tropamid, Bilim İlaç, Türkiye) and 2.5% phenylephrine (Mydfrin, Alcon, USA) were applied two or three times every five minutes to achieved pupil dilation. Following topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine, Alcon, USA), all infants underwent fundus examination using a binocular indirect ophthalmoscope with a 20 D and/or 28 D lens. Documentation of findings was based on the International Classification of ROP, third edition (ICROP-3).[15] Infants were followed according to the presence and severity of ROP.

STATISTICAL ANALYSIS

SPSS (SPSS Inc., Chicago, Illionis, USA) version 25.0 was used for statistical analysis. Findings were presented as mean±standard deviation (SD) for descriptive variables, as number (n) and percentage (%) for categorical variables. Normality assessment of continuous variables was made with Kolmogorov-Smirnov test and Shapiro-Wilk test. Normally distributed data were analyzed using Student's t-test, and non-normally distributed data were analyzed using the Mann-Whitney U test. Chi-square test was used to analyze categorical data. The relationship between risk factors (gender, GA, BW, PMA at examination, singleton or multiple pregnancies) and development of ROP was analyzed using logistic regression analysis. p value ≤0.05 was considered statistically significant.

RESULTS

Of the 2,364 preterm infants, 1,160 (49.07%) were singleton pregnancies and 1,204 (50.93%) were multiple pregnancies. The mean GA and BW in singleton

and multiple pregnancies were 34±1.00 weeks, 2,134±454 g and 33±1.00 weeks, 1,961±326 g, respectively. GA and BW were significantly lower in multiple pregnancies (p=0.000 for GA; p=0.003 for BW). Of the singleton and multiple pregnancies, 518 (44.7%) and 576 (47.8%) were female, respectively (p=0.120). The examination was performed at a mean PMA of 37.95±2.71 weeks (35 to 92 weeks) in singleton pregnancies and 38.27±7.85 weeks (35 to 196 weeks) in multiple pregnancies (p=0.083). ROP was detected in 3.13% (n=74) of the infants; 0.85% (n=20) of these were singleton pregnancies and 2.28% (n=54) were multiple pregnancies. While ROP did not develop in 1,140 out of 1,160 infants in singleton pregnancies, Stage I ROP was observed in 19 (1.6%) infants and Stage II ROP was observed in 1 (0.1%) infant. Again, while ROP did not develop in 1,150 out of 1,204 infants in multiple pregnancies, Stage I ROP was observed in 47 (3.9%) infants and Stage II ROP was seen in 7 (0.6%) infants. The development of ROP in multiple pregnancies was significantly higher than in singleton pregnancies (p=0.000). Table 1 summarizes the infants' demographic data and ROP findings.

While there was no significant relationship between gender and the development of ROP in univariate analysis (β=0.811, p=0.375), GA, BW, PMA at examination and multiple pregnancy were significantly associated with ROP (β=0.436, p=0.000; β=0.998, p=0.000; β=0.637, p=0.000; β=2.677, p=0.000, respectively). In multivariable analysis, GA (β=0.554, p=0.000), BW (β=0.999, p=0.001) and multiple pregnancy (β=2.375, p=0.001) were significantly associated with the development of ROP. The results of the logistic regression analysis are presented in Table 2.

TABLE 1: Demographic data and ROP findings of infants.

	Singleton pregnancy (n=1,160)	Multiple pregnancy (n=1,204)	p value
Gestational age (week) ($\bar{X}$±SD)	34±1.00	33±1.00	**0.000****
Birth weight (g) ($\bar{X}$±SD)	2,134±454	1,961±326	**0.003****
Gender (female/male) (n)	518/642	576/628	0.120*
PMA at examination (week) ($\bar{X}$±SD)	37.95±2.71	38.27±7.85	0.083**
ROP Outcome, n (%)			
ROP present	20 (0.85)	54 (2.28)	**0.000***
ROP absent	1,140 (48.22)	1,154 (48.81)	
Zone of ROP, n (%)			
Zone II	6 (0.5)	22 (1.8)	0.398*
Zone III	14 (1.2)	32 (2.7)	
Stage of ROP, n (%)			
Stage I	19 (1.6)	47 (3.9)	0.327*
Stage II	1 (0.1)	7 (0.6)	

*Chi-square test; **Mann- Whitney U test; ROP: Retinopathy of prematurity; SD: Standard deviation; PMA: Postmenstruel age.

TABLE 2: Logistic regression analysis of risk factors related with ROP development.

	Univariable regression analysis		Multivariable regression analysis	
	β (95 CI)	p value	β (95 CI)	p value
Gender	0.811	0.375		
Gestational age	**0.436**	**0.000**	**0.554**	**0.000**
Birth weight	**0.998**	**0.000**	**0.999**	**0.001**
PMA at examination	**0.637**	**0.000**	0.955	0.549
Type of pregnancy				
Singleton Multiple	**2.677**	**0.000**	**2.375**	**0.001**

ROP: Retinopathy of prematurity; PMA: Postmenstrual age; CI: Confidence interval; Bold, statistically significant values are highlighted.

DISCUSSION

While this study found a significant association between multiple pregnancy and the development of ROP, GA and BW in late preterm infants, it also showed that GA, BW, and multiple pregnancies were independent risk factors for ROP in late preterm infants. Although GA and BW are the most important known risk factors for the development of ROP in both singleton and multiple pregnancies, the effect of multiple pregnancies as a risk factor is still a controversial issue. Tseng et al. found that the incidence of ROP was significantly higher in twin pregnancies ($p<0.0001$). When they compared it according to BW, they stated that the incidence of ROP was higher in twins with normal BW [95% confidence interval (CI)=10.8-20.4] and in twins under 1,000 g compared to singletons (95% CI=1053-2067).[2] In another study with 229 preterm infants, the incidence of ROP was found to be significantly higher in multiple pregnancies (51.2%) than in singletons (36.7%) (odds ratio, 1.81; 95% CI, 1.05-3.13; $p=0.033$).[16]

Contrary to these findings, Dabir et al. found that the development of ROP in premature infants screened within the scope of a multicenter project between 2019 and 2021 was significantly higher in singleton pregnancies (24.1%) than in multiple pregnancies (16.5%) ($p=0.004$).[12] Similarly, Friling et al. evaluated the effect of the number of pregnancies on ROP in 363 infants with BW≤1,500 g and found that the frequency of advanced stage ROP (Stage II and Stage III) was significantly higher in singleton pregnancies than in multiple pregnancies ($p=0.024$).[17] In a study from Iran, it was stated that although the frequency and severity of ROP were more evident in singleton pregnancies, no significant difference was found between singleton and multiple pregnancies. It was stated that these results may be due to risk factors such as BW and GA rather than the type of pregnancy, and that single and multiple pregnancies can be screened in accordance with standard protocols.[11]

On the other hand, there are also studies reporting that the incidence of ROP is similar in singleton and multiple pregnancies. Blumenfeld et al. found that 46% of multiple pregnancies, 45% of singleton pregnancies had ROP, and the percentage of Stage 1, 2 or 3 or threshold ROP were similar in singleton and multiple pregnancies.[13] Again, Friling et al. compared 99 preterm infants born with multiple pregnancies with a BW of ≤1,500 g and infants born with singleton pregnancies and found that the incidence of ROP did not differ between singleton and multiple pregnancies. They also stated that the most important factor in the development of ROP is very low BW rather than the type of pregnancy.[14]

As expected, although many factors play a role in the development of ROP, ROP is more common in premature infants with a low BW and GA. It is also known that the risk of early GA, low BW and preterm birth is higher in multiple pregnancies than in singleton pregnancies. For this reason, an increase in the number of infants with ROP can be observed.[18] On the other hand, although in developed countries ROP is largely a problem of premature infants with GA≤32 weeks, recent studies have shown that ROP can develop in more mature and heavier premature infants in developing countries.[3-5,19,20] Therefore, we aimed to investigate the role of number of pregnancies on ROP in late preterm infants. In our study, similar to the study of Alsammahi and Basheikh we found that the incidence of ROP in multiple pregnancies was higher than in singletons, and that multiple pregnancies played an important role in the development of ROP. However, we found this difference in late preterms.[16]

Compared to previous studies, the strength of our study is that many risk factors that may affect the development of ROP were excluded by evaluating late preterm infants without perinatal risk factors. In this way, the actual effect of BW and GA as well as pregnancy type on ROP can be determined.

However, our study has some limitations. First of all, the late preterm group is a small group among preterm infants and it may not be appropriate to generalize the findings to the preterm population. Second, the number of infants included in our study was small. The third was the retrospective design of the study. On the other hand, it should be considered that the difference in GA and BW between the groups

may have a major impact on the development of ROP, and multiple or singleton births may make it difficult to evaluate the risk of ROP development. Larger and prospective studies are needed to evaluate this relationship in the future.

CONCLUSION

In conclusion, this study supports that multiple pregnancies may cause preterm birth and low BW in late preterm infants and may play a role in the development of ROP. Therefore, it may be appropriate to examine late preterm infants for ROP at least once, especially in developing countries.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Eşay Kıran Yenice; **Design:** Eşay Kıran Yenice; **Control/Supervision:** Eşay Kıran Yenice, Caner Kara; **Data Collection and/or Processing:** Eşay Kıran Yenice; **Analysis and/or Interpretation:** Eşay Kıran Yenice, Caner Kara; **Literature Review:** Eşay Kıran Yenice; **Writing the Article:** Eşay Kıran Yenice; **Critical Review:** Eşay Kıran Yenice, Caner Kara; **Materials:** Eşay Kıran Yenice, Caner Kara.*

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