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Original Article / Özgün Araştırma

Effects of Breastfeeding and Perinatal Factors on Development of Retinopathy of Prematurity

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Abstract

Objective: Breastfeeding is very important for the development and well-being of an infant. Other perinatal factors also influence the well-being of the infant like the method of conception, delivery method and multiple pregnancy. Our aim in this study is to investigate the effects of these factors on the development of retinopathy of prematurity (ROP).

Methods: The records of premature infants who were screened for ROP between 2015 and 2018. Gestational age (GA), birth weight (BW), sex, time spent in neonatal intensive care unit (NICU), assisted reproduction method, method of delivery, breastfeeding and multiple births were noted. The presence of ROP, stage and zone of the disease, treatment for ROP were recorded.

Results: GA and BW were significantly lower and time spent in NICU was significantly longer in infants with ROP ($p<0.001$). Only breastfed patients had a lower rate of ROP than other groups, however they had significantly higher GA, BW and lower time in NICU. Assisted conception significantly decreased the presence of any stage ROP ($p=0.037$). Delivery method and multiple pregnancy didn't have an effect on the presence of ROP.

Conclusion: Low GA, low BW and more time spent in NICU are the major risk factors for development of ROP. The relation between ROP and breastfeeding is not reliable because of the significant difference of BW, GA and time spent in NICU that exists between the only breastfed group and others. Assisted reproductive techniques decreased the incidence of ROP which might be due to the advances in the assisted reproduction methods.

Keywords: Retinopathy of prematurity, breastfeeding, assisted reproduction, delivery method, multiple pregnancy

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Anne Sütü ve Perinatal Faktörlerin Prematüre Retinopatisi Gelişimi Üzerindeki Etkileri

Öz

Amaç: Anne sütü, bir bebeğin büyüme ve gelişiminde çok önemli bir yere sahiptir. Yardımcı üreme yöntemleri, doğum şekli ve çoğul gebelik de bebeğin sağlığını etkileyebilen perinatal faktörlerdendir. Bu çalışmadaki amacımız anne sütü, konsepsiyon yöntemi, doğum şekli ve çoğul gebeliğin prematüre retinopatisi (PR) gelişimi üzerindeki etkilerini araştırmaktır.

Yöntemler: Prematüre doğum nedeniyle 2015 ve 2018 yılları arasında PR taraması yapılan bebeklerin kayıtları incelendi. Doğum haftası (DH), doğum ağırlığı (DA), yenidoğan yoğun bakım ünitesinde (YDYBÜ) yatış süresi, yardımcı üreme tekniği, doğum şekli, anne sütü alımı ve çoğul gebelik not edildi. Prematüre retinopatisi varlığı, hastalığın zonu ve evresi, tedavi gereksinimi ve gelişen sekeller kayıt edildi.

Bulgular: Prematüre retinopatisi saptanan hastalarda DA ve DH diğer hastalara göre anlamlı olarak düşük, YDYBÜ yatış süresi anlamlı olarak daha uzundu ($p<0.001$). Sadece anne sütü alan bebeklerde PR görülme oranı diğerlerine göre daha düşüktü fakat sadece anne sütü alan bebeklerin DH ve DA diğerlerine göre daha yüksek, YDYBÜ yatış süresi daha düşüktü. Yardımcı üreme teknikleri PR insidansını anlamlı olarak düşürdü ($p=0.037$). Doğum şekli ve çoğul gebelik varlığı PR gelişimini etkilemedi.

Sonuç: Düşük DA, düşük DH ve YDYBÜ geçen süre PR gelişiminde en önemli risk faktörleridir. Anne sütü ile PR arasında tespit edilen anlamlı ilişki iki grup arasında DA, DH ve YDYB'da yatış süreleri anlamlı olarak farklı olduğundan güvenilir değildir. Çoğul gebelik ve doğum şeklinin PR gelişimi üzerinde etkisi saptanmamıştır. Yardımcı üreme tekniklerinin PR insidansını azalttığı görülmüş olup bu durum yardımcı üreme tekniklerindeki gelişmelere bağlanabilir.

Anahtar kelimeler: Prematüre retinopatisi, anne sütü, yardımcı üreme teknikleri, doğum şekli, çoğul gebelik.

INTRODUCTION

Breastfeeding is very important for the development and well-being of an infant[1]. It has antibodies like secretory IgA, IgM and IgG which protect the child from infections[2]. It contains growth factors and hormones which help the development of the infant[3]. It also includes a healthy microbiome like Bifidobacteria and Lactobacilli which produces an intestinal barrier inhibiting pathogen binding and inflammatory responses[2,4]. Women are advised to breastfeed exclusively for at least 6 months. According to previous research breastfed infants develop less infections[5], they have better neurological outcome[6], it reduces the risk of sudden infant death syndrome[7], it decreases the risk of childhood leukemia[8] and protects against obesity and diabetes[9,10]. Previous studies evaluated the effects of breastfeeding on the development of retinopathy of prematurity (ROP). Some studies reported that breastfeeding decreases incidence of ROP[11] while others disagreed[12].

Other perinatal factors also influence the well-being of the infant like the method of conception, method of delivery and multiple pregnancy. There are studies with conflicting results about the effects of these factors on ROP development[13]. Our aim in this study is to investigate the effects of breastfeeding, method of conception, method of delivery and multiple pregnancy on the development of ROP.

METHODS

The study was approved by the ethics committee and research adhered to the tenets of the Declaration of Helsinki. The records of premature infants who were screened for ROP between 2015 and 2018 in our hospital were included in this study. Screening for ROP was performed to infants with gestational age (GA) less than 32 weeks, birth weight less than 1500 gr or who were hospitalized in neonatal

intensive care unit for any reason. First examination was done at 4 weeks postnatally for infants with a GA of more than 27 weeks and at 31 weeks postmenstrual age for infants with a GA of less than 27 weeks using an indirect ophthalmoscope. The classification of ROP and the decision for the treatment were done according to the criteria determined by early treatment for retinopathy of prematurity study group[14]. Gestational age, birth weight, sex, time spent in NICU, any assisted reproduction method, method of delivery, breastfeeding and multiple births were noted. The presence of ROP, stage and zone of the disease, treatment for ROP and any adverse event regarding ROP were recorded. Patients with missing data were excluded from the study.

Analysis

Statistical analysis was done using SPSS v.22.0 for Windows (SPSS, Inc. Chicago, IL, USA). Chi-square test was used to evaluate the ordinal data; if there was a significant difference, posthoc tests was used to define the groups which were significantly different. Independent samples t-test and Mann-Whitney U test were used to compare the mean values between groups. Significance was assumed at a P value <0.05.

RESULTS

Data of 407 patients were included in this study. Patient demographics are shown in Table 1. Gestational age and birth weight were significantly lower and time spent in NICU was significantly longer in infants with ROP (Table 2). There wasn't a significant difference between patients who were breastfed and who weren't regarding the presence of ROP (p=0.052). However, we detected a significant difference regarding the presence of ROP according to nutrition status when we divided the patients into 3 groups (Table 3). Posthoc tests revealed that only breastfed patients had a lower rate of ROP than other groups, however the patients in the only breastfed group had significantly higher gestational age, birth weight and lower time in NICU. Breastfeeding did not has an effect on the development of treatment requiring ROP when evaluated within any-stage ROP patients (p=0.258).

Table 1. Patient demographics

	n (%)	Mean ± SD
Gestational age (weeks)	407 (100)	31.9 ± 2.9
Birth weight (gr)	407 (100)	1733.8 ± 546.1
Time spent in NICU (days)	407 (100)	36.0 ± 24.5
Sex		
Male	209 (51.4)	
Female	198 (48.6)	
Assisted conception method		
Present	55 (13.5)	
Absent	352 (86.5)	
Delivery method		
Vaginal delivery	75 (18.4)	
Cesarean section	332 (81.6)	
Multiple pregnancy		
Absent	249 (61.2)	
Twin	141 (34.6)	
Triplet	15 (3.7)	
Quintuplets	2 (0.5)	
Breastfeeding		
Only breastfeeding	62 (15.2)	
Only formula	92 (22.6)	
Breastfeeding and formula	253 (62.2)	
ROP		
Absent	191 (46.9)	
Mild ROP	118 (29)	
Type 2 ROP	12 (2.9)	
Type 1 ROP	86 (21.1)	

ROP, retinopathy of prematurity; NICU, neonatal intensive care unit; SD, standard deviation; n, number

Assisted conception significantly decreased the presence of any stage ROP (Table 4) and there wasn't any difference regarding the gestational age, birth weight and time spent in NICU between assisted conception present and absent patients. Among the any-stage ROP patients assisted conception had no effect on the development of treatment requiring ROP (p=0.593). Assisted reproductive techniques caused an increased incidence of multiple pregnancy (p<0.001).

Table 2. Gestational age, birth weight and time spent in neonatal intensive care unit in patients with or without retinopathy of prematurity

	No ROP	Any-stage ROP	p
Gestational age (weeks)	33.3 ± 2.5	30.7 ± 2.7	<0.001
Birth weight (gr)	1984.6 ± 552.4	1509.9 ± 432.2	<0.001
Time spent in NICU (days)	27.7 ± 23.0	43.3 ± 23.5	<0.001

ROP, retinopathy of prematurity; NICU, neonatal intensive care unit

Table 3. Retinopathy of prematurity presence according to nutrition status

	Only breastfeeding n (%)	Breastfeeding and formula n (%)	Only formula n (%)
ROP absent	36 (8.8%)	120 (29.5%)	35 (8.6%)
Any stage ROP	26 (6.4%)	133 (32.7%)	57 (14.0%)

p=0.048; ROP, retinopathy of prematurity; n, number

Table 4. Retinopathy of prematurity presence according to assisted conception status.

	Assisted conception present, n (%)	Assisted conception absent, n (%)
ROP absent	33 (8.1%)	158 (38.8%)
Any stage ROP	22 (5.4%)	194 (47.7%)

p=0.037; ROP, retinopathy of prematurity; n, number

Delivery method and presence of multiple pregnancy did not have an effect on the presence of any-stage ROP (Table 5, Table 6) and treatment requiring ROP among the ROP patients (p=0.563, p=0.890, respectively).

Table 5. Retinopathy of prematurity presence according to delivery method.

	Normal vaginal delivery, n (%)	Cesarean section, n (%)
ROP absent	30 (7.4%)	161 (39.6%)
Any stage ROP	45 (11.0%)	171 (42.0%)

p=0.183; ROP, retinopathy of prematurity; n, number

Table 6. Retinopathy of prematurity presence according to multiple birth.

	Single birth, n (%)	Multiple birth, n (%)
ROP absent	118 (29.0%)	73 (17.9%)
Any stage ROP	131 (32.2%)	85 (20.9%)

p=0.815; ROP, retinopathy of prematurity; n, number

DISCUSSION

Breastfeeding is very important for the growth and development of an infant[1,4]. Human milk includes many antibodies, growth factors and microbiome which helps the healthy development of an infant. Lack of breastfeeding is associated with lots of diseases like leukemia8 and diabetes[9,10]. The role of breastfeeding in the development of ROP has been investigated in previous studies. Ginovart et al. reported that human milk reduces the risk of stage 2 and 3 ROP development[11]. Bharwani et al. showed that human milk intake protects from any-stage ROP and severe ROP in a recent meta-analysis[15]. Hylander et al. showed that human milk intake decreases the incidence of ROP in very low birth weight infants[16]. On the other hand Heller et al. reported that human milk does not have an effect on the incidence of severe ROP in extremely low birth weight infants[12]. Kao et al. showed that breastfeeding is not associated with presence of ROP[17]. Breastfeeding without formula significantly decreased the presence of any-stage ROP in our study, however the patients in the only breastfed group had significantly higher gestational age, birth weight and lower time in NICU. This may be due to the fact that infants with lower gestational age and birth weight spend more time in the NICU which interrupts the breastfeeding process and increase the need for additional formulas. Since these are major risk factors for the development of ROP we could not conclude that breastfeeding has an effect on ROP development. Additionally there wasn't a significant relation between the development of treatment requiring ROP and breastfeeding among the patients with any stage ROP in spite of the significant difference of gestational age and birth weight between the breastfed infants and the ones who took human milk and formula remained same. These results supports the conclusion that human milk intake does not have an effect on the presence of ROP.

Multiple pregnancies increase the risk of low birth weight and preterm birth so it may be a risk factor for the development of ROP[18]. Li et al. reported multiple pregnancy as a risk factor for ROP[19]. Similarly Martinez-Cruz et al. found a higher incidence of ROP in multiple pregnancy infants[20]. On the other hand Friling et al. reported that incidence of ROP is higher in singletons than multiple pregnancies[21]. In our study we didn't find a difference between singletons and multiple pregnancies regarding the presence of any-stage or treatment requiring ROP.

Assisted reproductive techniques are used more commonly by the couples who want to have children. Assisted reproductive techniques increase the risk of low birth weight, preterm birth, being small for gestational age and admission to NICU[22], which are major risk factors for ROP[23]. The effects of assisted reproduction on the development of ROP have been studied previously. Barker et al. couldn't find an association between assisted reproduction and ROP incidence[24]. Similarly Friling et al. reported that assisted reproduction is not related with ROP[21]. Chan et al. found that assisted reproductive techniques increase the risk for treatment requiring ROP[25]. We also detected a significant relation between assisted reproduction and ROP, however our results showed that assisted reproduction decreased the incidence of any-stage ROP. This might be because of the improvement of the methods of assisted reproductive techniques which in turn resulted in less number of multiple pregnancies and preterm birth[26].

The effects of delivery method on the presence of ROP have been investigated by previous studies. Manzoni et al. reported that vaginal delivery increases the risk of ROP development[27]. Abdel et al. didn't find a relation between mode of delivery and development of ROP[28]. Similarly we did not detect any association between delivery method and presence of any-stage or treatment requiring ROP.

In conclusion, low birth weight, low gestational age and more time spent in NICU where the infants are given oxygen are the major risk factors for development of ROP. The significant relation we found between the presence of any-stage ROP and breastfeeding is not reliable because of the significant difference of birth weight, gestational age and time spent in NICU that exists between the only breastfed group and infants with formula intake. There wasn't a relation between multiple pregnancy, delivery method and development of any-stage or treatment requiring ROP. Our results showed that assisted reproductive techniques decrease the incidence of ROP which might be due to the advances in the assisted reproduction methods. Further studies are needed to fully understand this relation.

Declaration of Conflicting Interests: The authors declare that they have no conflict ofinterest.

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KAYNAKLAR

1. Goldman AS. Evolution of immune functions of the mammary gland and protection of the infant. Breastfeeding Medicine. 2012; 7: 132–42.

2. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatric Research. 2007; 61: 2–8.

3. Savino F, Liguori SA. Update on breast milk hormones: leptin, ghrelin and adiponectin. Clinical Nutrition. 2008; 27: 42–7.

4. Dieterich CM, Felice JP, O'Sullivan E, Rasmussen KM. Breastfeeding and health outcomes for the mother-infant dyad. Pediatr Clin North Am. 2013; 60: 31-48.

5. Chien PF, Howie PW. Breast milk and the risk of opportunistic infection in infancy in industrialized and non-industrialized settings. Advances in Nutritional Research. 2001; 10: 69–104.

6. Kramer MS, Aboud F, Mironova E, et all. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry. 2008; 65: 578–84.

7. Hauck FR, Thompson JM, Tanabe KO, Moon RY, Vennemann MM. Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis. Pediatrics. 2011; 128: 103–10.

8. Kwan M, Buffler P, Abrams B, Kiley VA. Breastfeeding and the risk of childhood leukemia: a meta-analysis. Public Health Rep. 2004; 119: 521–35.

9. Li R, Grummer-Strawn LM, Fein SB. Do infants fed from bottles lack self-regulation of milk intake compared with directly breastfed infants? Pediatrics. 2010; 125: e1386–e93.

10. Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG. Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence. Am J Clin Nutr. 2006; 84: 1043–54.

11. Ginovart G, Gich I, Verd S. Human milk feeding protects very low-birth-weight infants from retinopathy of prematurity: a pre-post cohort analysis. J Matern Fetal Neonatal Med. 2016; 29: 3790-5.

12. Heller CD, O'Shea M, Yao Q et all. Human milk intake and retinopathy of prematurity in extremely low birth weight infants. Pediatrics. 2007; 120: 1-9.

13. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Surv Ophthalmol. 2018; 63: 618-37.

14. Early Treatment for Retinopathy Of Prematurity Cooperative Group: Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003; 121: 1684–94

15. Bharwani SK, Green BF, Pezzullo JC, et all. Systematic review and meta-analysis of human milk intake and retinopathy of prematurity: a significant update. J Perinatol. 2016; 36: 913-20.

16. Hylander MA, Strobino DM, Pezzullo JC, Dhanireddy R. Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants. J Perinatol. 2001; 21: 356-62.

17. Kao JS, Dawson JD, Murray JC et all. Possible roles of bilirubin and breast milk in protection against retinopathy of prematurity. Acta Paediatr. 2011; 100: 347-51.

18. Shiozaki A, Yoneda S, Nakabayashi M et all. Multiple pregnancy, short cervix, part-time worker, steroid use, low educational level and male fetus are risk factors for preterm birth in Japan: a multicenter, prospective study. J Obstet Gynaecol Res. 2014; 40: 53-61.

19. Li WL, He L, Liu XH, Wang YM, Liu JQ. Analysis of risk factors for retinopathy of prematurity. Int J Ophthalmol. 2011; 4: 631-3.

20. Martínez-Cruz CF, Salgado-Valladares M, Poblano A, Trinidad-Pérez MC. Risk factors associated with retinopathy of prematurity and visual alterations in infants with extremely low birth weight. Rev Invest Clin. 2012; 64: 136-43.

21. Friling R, Axer-Siegel R, Hersocovici Z, et all. Retinopathy of prematurity in assisted versus natural conception and singleton versus multiple births. Ophthalmology. 2007; 114: 321-4.

22. Sutcliffe AG, Ludwig M. Outcome of assisted reproduction. Lancet. 2007; 370, 351–59.

23. Gebeşçe A, Uslu H, Keleş E et all. Evaluation of very low birth weight infants in the neonatal intensive care unit of a university hospital. Dicle Med J 2015; 42: 137-42.

24. Barker L, Bunce C, Husain S, Adams GG. Is artificial reproductive technology a risk factor for retinopathy of prematurity independent of the generation of multiple births? Eur J Ophthalmol. 2017; 27:174-8.

25. Chan RV, Yonekawa Y, Morrison MA et all. Association between assisted reproductive technology and advanced retinopathy of prematurity. Clin Ophthalmol. 2010; 4: 1385-90.

26. Funnell CL, Dabbs TR. Assisted conception and retinopathy of prematurity: 8-year follow-up study. Eye (Lond). 2007; 21:383-6.

27. Manzoni P, Farina D, Maestri A et all. Mode of delivery and threshold retinopathy of prematurity in pre-term ELBW neonates. Acta Paediatr. 2007; 96: 221-6.

28. Abdel HA, Mohamed GB, Othman MF. Retinopathy of Prematurity: A Study of Incidence and Risk Factors in NICU of Al-Minya University Hospital in Egypt. J Clin Neonatol. 2012; 1:76-81.