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The importance of timely ophthalmologic examination in preterm infants at risk of retinopathy occurrence

Značaj pravovremenog oftalmološkog pregleda kod nedonoščadi sa prisutnim rizikom od pojave retinopatije

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Abstract

Background/Aim. Retinopathy of prematurity (ROP) is a multifactorial disease in premature infants. The aim of this study was to determine the incidence of ROP in children treated at the Center of Neonatology, Pediatric Clinic, Clinical Center in Kragujevac, Serbia. **Methods.** The study covered all children with birth weight below 2,000 g and/or gestational age below the 37th week, who from June 2006 to December 2009 underwent ophthalmological examination for ROP. The results of fundoscopy were classified in accordance with the International Classification of ROP. The treatment of infants and those with ROP was conducted in accordance with the early treatment of ROP study recommendations. We analyzed gestational age, birth weight and postconceptional age in two groups: healthy infants and those with severe form of ROP. Statistical analysis was performed using the SPSS 16. **Results.** A total of 478 children met the criteria of screening for ROP. Severe stage of ROP, which required laser treatment, had 102 (21.3%) children. Out of the infants with severe ROP 14 (13.7%) of the infants with APD had aggressive posterior disease, while two (0.4%) remained blind. The differences in the mean values of gestational age between the healthy and the children with severe form of the disease were statistically significant ($p < 0.0005$). The mean value of gestational age for the healthy children was 33.33 ± 2.28 weeks and for the seek infants 30.66 ± 2.79 weeks. The mean value of the weight in healthy children was 1.981 ± 407 g, and in sick children 1.535 ± 434 g which was statistically significant ($p < 0.0005$). Multivariate binary logistic regression showed that the occurrence of the disease depends on body weight and gestational age. **Conclusion.** The incidence of severe forms of ROP was 21.3%. Aggressive form of ROP was present in 13.7% of the children. The cut-off value for body weight was 1.740 g, and for gestationl age 32.5 weeks.

Key words:
retinopathy of prematurity; infant, premature; gestational age; birth weight; incidence; serbia.

Apstrakt

Uvod/Cilj. Retinopatija prematuriteta (ROP) je multifaktorijalna bolest prevremeno rođene dece. Cilj ove studije bio je da se utvrdi incidencija retinopatije prematuriteta kod lečenih u Centru za neonatologiju Klinike za pedijatriju, Kliničkog centra u Kragujevcu. **Metode.** Kod sve dece telesne mase na rođenju ispod 2 000 g i/ili gestacione starosti ispod 37 nedelja, u periodu od juna 2006. do decembra 2009. godine, urađen je oftalmološki pregled na retinopatiju prematuriteta. Rezultati oftalmološkog pregleda su klasifikovani prema Internacionalnoj klasifikaciji za retinopatiju prematuriteta. Lečenje dece sa retinopatijom vršeno je laserom prema preporukama studija za rano lečenje. Analizirali smo gestacionu starost, telesnu masu na rođenju i postkoncepcijsku starost dve grupe: zdrava deca i deca sa teškom formom retinopatije. Statistička analiza rađena je korišćenjem programa SPSS 16. **Rezultati.** Ukupno 478 dece je ispunilo kriterijume skrininga za retinopatiju prematuriteta. Tešku formu retinopatije koja je zahtevala lečenje laserom imalo je 102 (21,3%) dece. Od dece sa teškom formom ROP, 14 (13,7) je imalo agresivnu formu, dok je dvoje (0,4%) dece sa agresivnom formom ostalo slepo. Razlika srednjih vrednosti gestacione starosti između zdrave dece i dece sa teškom formom retinopatije bila je statistički značajna ($p < 0,0005$). Srednja vrednost gestacione starosti zdrave dece bila je 33,33 ± 2,28 nedelje, a bolesne 30,66 ± 2,79 nedelje. Srednja vrednost telesne mase zdrave dece bila je 1 981 ± 407 g, a bolesne 1 535 ± 434 g, što je bilo statistički značajno ($p < 0,0005$). Multivarijantna binarna logistička regresija pokazala je da na pojavu bolesti veliki uticaj ima telesna masa i gestaciona starost dece. **Zaključak.** Incidencija teške forme ROP iznosila je 21,3%. Agresivan oblik ROP imalo je 13,7% dece. Granična vrednost za telesnu masu iznosila je 1 740 g, a za gestacionu starost 32,5 nedelja.

Ključne reči:
retinopatija kod prematurusa; nedonošče; gestacijska starost; telesna masa, rođenje; incidenca; srbija.

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Introduction

Retinopathy of prematurity (ROP) is a proliferative disease of immature retina that may cause severe sight damage or blindness [1–3]. Incidence of ROP and blindness in newborns depends on the level of care and methods used in neonatal intensive care units (NICU), and also more recently on economic development of a country [4].

Two epidemics of ROP were recorded in developed countries in the past. The first one was in 1940s and 1950s, where the main causative factor was supplemental use of oxygen [4–5]. Second epidemic occurred in 1970s, due to increased survival rate of extremely prematurely born babies [4–6]. Recently, a "third epidemic" appeared in the developing countries [7]. Possible causes of the "third epidemic" were: increase in rate of preterm birth, increased survival rate of preterm babies due to development of NICUs; wider screening criteria. The babies are being exposed to less controlled risk factors than in developed countries. Like in the first epidemic, the babies affected in the third one were within wider range of birth weights (BW) and gestational ages (GA) [4, 8–11].

Interestingly, both countries with high and low infant mortality rate (IMR) (> 60/1000 live births and < 9/1000 live births, respectively) do not record blindness caused by ROP, or it is very rare. In the countries with IMR between 9 and 60 per 1,000 live births, ROP emerges as an important cause of blindness [4]. In Serbia, the infant mortality rate is 14/1000 live births (national statistics for 2008), but there are no accurate data at the national level that would identify ROP as possible cause of blindness [12]. In order to prevent blindness due to ROP in countries like Serbia, ophthalmological screening of all newborns with risk of premature retinopathy should be conducted. However, screening criteria are different and subject to change in various countries [12], and there exists the need at the national level to carefully review, revise and adapt these various screening guidelines to the context of the ROP situation in Serbia.

During the revision of international classification of ROP in 2005, the aggressive posterior disease (APD) was included in it [13]. The APD is more commonly seen in infants with BW less than 1,200 g, or with gestational age below 24 weeks. However, in the countries like Serbia, it is also present in infants with bigger BW and older than 24 weeks of GA. This disease is very aggressive, progresses rapidly and may cause retinal detachment and blindness. It requires rapid diagnostics and immediate treatment [12–17].

The aim of this study was to estimate the incidence of ROP and to verify the applicability of national guidelines for screening in our country undergoing socio-economic transition.

Methods

The Neonatology Center of Pediatric Clinic in Kragujevac, Serbia, is an interregional center admitting high-risk infants from an area of 10 municipalities in Serbia. All infants admitted from June 2006 to December 2009 to the facility, with BW under 2000 g and/or GA under 37 weeks were submitted to screening [12]. Screening was conducted outside these criterions in cases with high risk of ROP development, such as respiratory distress.

The first ophthalmologic examination was done between the 4th and the 5th postnatal week. Fundoscopy was performed after dilatation of the pupils. We used 2.5% phenylephrine or 0.5% cyclopentolate drops three times per hour before examination, in order to achieve maximal dilatation of the pupils. Binocular indirect ophthalmoscope with condensing 20 D lens and an indenter was used for the examination. The results of fundoscopy were classified in accordance with the International Classification of Retinopathy of Prematurity (ICROP) [13]. This classification includes three parameters: localization of changes at retina, dilatation of pathologically changed blood vessels and stage of pathologically changed vascularisation.

After the first ophthalmological examination all newborns with normal findings were excluded from further follow-up. We continued to monitor newborns with undeveloped retinal blood vessels, but without signs of ROP, every 7 to 14 days. The treatment of newborns with ROP was conducted in accordance with Early Treatment of ROP (ETROP) study recommendations, which stressed necessity of discovering "prethreshold disease" and early treatment [13]. According to this study, ROP that needs treatment is type 1 ROP: zone I, any ROP stage with plus disease; zone I, stage 3 of ROP without plus disease; and zone II, stage 2 or 3 of ROP with plus disease [13]. Type 2 ROP requires follow-up visit: zone 1, stage 1–2 without plus, zone 2, stage 3 without plus.

During ophthalmological examination we searched for significant dilatation and tortuosity of both vessel types in the first zone, in all four quadrants. The APD appears much earlier than classical ROP, already after three weeks of postnatal age. The APD does not follow the classical pattern of stage 1 through stage 5.

We analyzed the post conceptual age (PCA) in all the groups. PCA is defined as actual postnatal age in weeks (days) minus difference of 40 weeks of gestation and gestation at birth. PCA refers to the time of screening, i.e. first ophthalmologic examination. All the children with AP ROP, the first exam marked the time of the first laser therapy.

Statistical analysis was performed using the Statistical Package for Social Sciences software, SPSS 16. The data are reported as means ± SD. The statistical significance of differences between the results was tested using a two-sided independent Student's *t*-test. The results were considered significantly different when $p \leq 0.05$. The independency between categorical variables was tested by the χ^2 test. The optimal data cut-off was determined by the receiver operating characteristic (ROC) curves. Such cut-off was used for computing sensitivity and specificity. Risk of retinopathy was tested by the multiple binary logistic regression.

Results

The study population consisted of 1223 infants admitted to the Neonatology Center. From this primary population, 478 infants had risk factors for retinopathy. The study group consisted of 273 (57.1%) male and 205 (42.9%) female infants.

After the first ophthalmologic examination, 131 (27.4%) infants had normally developed retinal blood vessels The other 347 (72.6%) infants had primarily undeveloped retinal blood vessels. Within this group that was subjected to further ophthalmological monitoring, 170 (35.6%) infants were found with insufficiently developed retinal blood vessels. They were added to the healthy group of 131 infants, and the total number of newborns with normally developed retinal blood vessels was 301 (62.9%). Seventy-five (15.7%) newborns developed stage 1 or 2 of ROP with spontaneous regression. They were added to the healthy infants, while 102 (21.3%) newborns developed severe stage of ROP, and underwent laser therapy (Figure 1).

The average values of GA, BW and PCA of 376 healthy infants and 102 infants with severe stage of ROP are shown in Table 1.

gestational age for the healthy children was 33.33 ± 2.28 weeks and for the seek infants 30.66 ± 2.79 weeks. Gestational age may be a marker (indicator) of the disease (retinopathy). The cut-off value was 32.5 weeks (Table 2). The sensitivity was 69.3% and the specificity 73.1%. The positive predictive value was 40.9 %, while the negative predictive value was 89.9 % (Figure 2).

The differences in the mean values of the weight between healthy and sick children were statistically significant ($p < 0.0005$). The mean value of the weight in the healthy children was 1,981 ± 407 g and in the sick children 1,535 ± 434 g. Birth weight in infants may be a marker of the disease (retinopathy) . The cut-off value was 1,740 g (Table 2). The sensitivity was 72.1%, and the specificity was 72.3%. The positive predictive value was 41%, and negative predictive value was 90.6% (Figure 3).

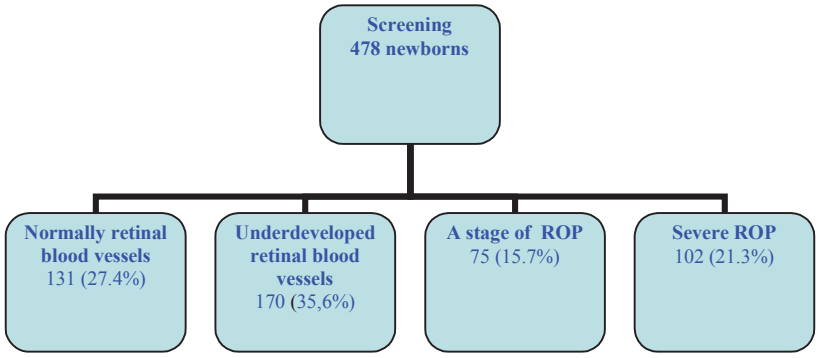

Fig. 1 – Division of premature infants according to the findings in the ophthalmologic examination; ROP – retinopathy of prematurity

Table 1

Primary characteristics of healthy infants (HI) and infants with severe retinopathy of prematurity (ROP)

Parameters	HI (n = 376)	ROP (n = 102)
	x̄ ± SD (min–max)	x̄ ± SD (min–max)
GA [weeks]	33.3 ± 2.3 (26–37)	30.66 ± 2.79 (25–37)
BW [g]	1980.6 ± 406.8 (770–2900)	1535 ± 434 (700–3200)
PCA [days]	245.5 ± 18.2 (210–287)	238.66 ± 19.56 (196–273)

GA – gestational age, BW – birth weight, PCA – post conceptual age

Table 2

Significance of gestational age (GA) and birth weight (BW) in the diagnosis of retinopathy of prematurity (ROP)

Parameters	Test	Infants (n)		Total
		with ROP	without ROP	
GA (weeks)				
< 32.5	positive	70	101	171
> 32.5	negative	32	275	307
Total		102	376	478
BW (g)				
< 1750	positive	74	105	179
> 1750	negative	28	271	299
Total		102	376	478

The differences in the mean values of gestational age between healthy and children with severe form of the disease were statistically significant ($p < 0.010$). The mean value of

Multivariate binary logistic regression showed that the occurrence of the disease depends on body weight ($p < 0.0005$) and gestational age ($p = 0.010$). The odds ratio

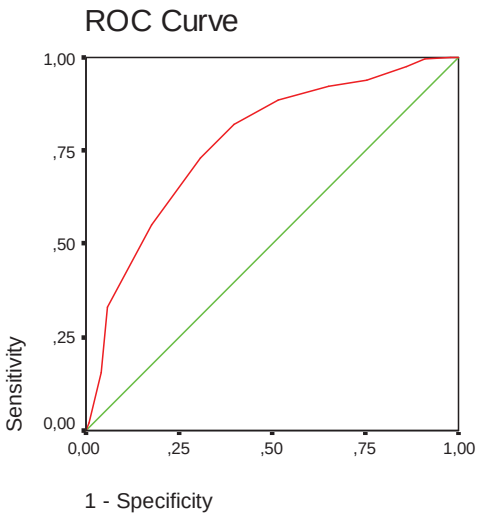

Fig. 2 – ROC curve showing discriminatory value of gestational age (GA) for identifying newborn infants at risk for retinopathy of prematurity (ROP)

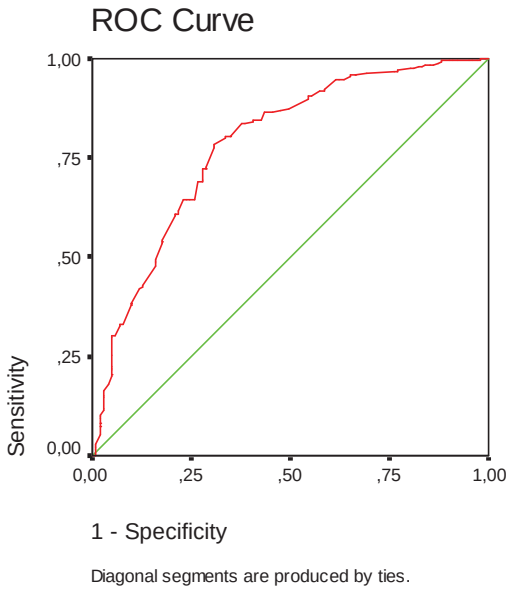

Fig. 3 – ROC showing discriminatory value of birth weight (BW) for identifying newborn infants at risk for retinopathy of prematurity (ROP)

for weight was 0.998 (0.997–0.999). One gram of additional weight reduces the risk of developing the disease by 0.2%. The odds ratio for gestational age was 0.840 (0.736–0.959). One additional week of gestation reduces the risk of developing the disease by 16% (Table 3).

Out of 102 infants with severe stage of ROP 14 (13.7%) developedAPD. Female and male gender was equally present. The average GA of infants with APD was 28.7 (25 to 33) weeks. The average body weight was 1,307.4 g (700 to 1,950) and when APD was diagnosed, PCA was 231.2 days (33 weeks). There were also two (0.4%) blind infants in the screened group, all of them with APD. Both infants had been laser treated immediately after the diagnosis of the disease, but the laser treatment was unsuccessful.

Discussion

ROP is a serious eye disorder that can lead to blindness [5]. Increased survival rate of premature infants requires screening and early treatment in order to control this disease [18]. The aim of screening is to detect all infants with ROP that require treatment. The CRYO-ROP study has defined the "threshold disease" of ROP as a stage when the treatment is necessary [19]. On the other hand, the ETROP study has shown that earlier treatment of highly risky "pre-threshold" stage of ROP leads to even better results [18].

Many countries have national guidelines for screening in relation to BW and GA in accordance with studies on ROP incidence [20–32]. In developing countries (including Serbia) the incidence of ROP is higher, especially among premature infants with higher BW and GA [23–24]. In Serbia, screening is recommended even though the official protocol for screening does not exist. Recommended screening includes infants with GA below 37 weeks and/or BW of 2,000 g or less, as well as newborns at high risk outside this criteria, as discussed in this paper.

The incidence of severe ROP that required laser therapy in our study was 21.45% of all the screened infants. In the group of infants that had laser therapy, the minimal GA was 25 weeks and maximal 37 weeks. BW was in the range from 700 g to 3,200 g. Such a wide range of BW and GA is typical for developing countries, which fall under the "third epidemic" of ROP.

This shows that we should not just follow strictly recommended criteria since the aim of the screening is to discover all newborns at risk for severe ROP. The percentage of severe ROP does not follow closely the percentage of screening, which is high. The American Academy of Pediatrics and the American Academy of Ophthalmology recommend screening in infants with BW of less than 1,500 g or GA of 30 weeks or less, as defined by the attending neonatologist. It also included the selected infants with birth weight between 1,500 g and 2,000 g or GA greater than 30 weeks with an unstable clinical course, as well as those requiring cardiorespiratory support, as determined by their attending pediatrician or neonatologist. UK retinopathy of pre-

Table 3

The influence of birth weight (BW) and gestational age (GA) on the occurrence of retinopathy of prematurity (ROP) (the results of multiple binary logistic regression)

Parameters	Odd ratio	Lower–upper limits	*p*
GA	0.840	0.736–0.959	0.010
BW	0.998	0.997–0.999	0.0005

maturity guideline suggests the following screening criteria: all babies less than 32 weeks GA or less than 1,501 g BW should be screened for ROP and all babies less than 31 weeks GA or less than 1,250 g BW must be screened for ROP [12, 24]. As an example of the need for careful adaptation of screening criteria to the local situation, if we had applied the UK screening criteria directly, we would have missed 31 infants with severe form of ROP, which required laser therapy.

The majority of countries recommend screening in the 4th postnatal week, *ie* between 31 and 34 post conceptional week [19, 23]. Because of early appearance of APD ROP, screening is recommended as early as 30–31 postconceptional week [31]. Screening before 30 weeks and laser therapy would be difficult to administer.

Conclusion

The incidence of severe form ROP in the studied population of our region is very high. Screening criteria applied in this work are much broader than in developed countries. We included all infants with BW under 2,000 g and/or GA under 37 weeks as well as infants outside these criteria in cases with high risk of ROP development. Applying the criteria from developed countries to our case series would have made us to omit a relatively large number of infants with severe form of ROP. In countries in transition, such is Serbia, the necessity for ROP screening is very high, as well as the need to create locally adapted screening criteria.

R E F E R E N C E S

1. *Hunter DG, Mukai S.* Retinopathy of prematurity: pathogenesis, diagnosis, and treatment. Int Ophthalmol Clin 1992; 32(1): 163−84.
2. *Gibson DL, Sheps SB, Uh SH, Schechter MT, McCormick AQ.* Retinopathy of prematurity-induced blindness: birth weight-specific survival and the new epidemic. Pediatrics 1990; 86(3): 405−12.
3. *Clark D, Mandal K.* Treatment of retinopathy of prematurity. Early Hum Dev 2008; 84(2): 95−9.
4. *Gilbert C.* Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 2008;84(2): 77−82.
5. *King MJ.* Retrolental fibroplasia; a clinical study of 238 cases. Arch Ophthal 1950; 43(4): 694−711.
6. *Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P,* et al. On behalf of the International NO-ROP Group. Characteristics of babies with severe retinopathy of prematurity in countries with low, moderate and high levels of development: implications for screening programmes. Pediatrics Electronic Pages 2005; 115: 518–25.
7. *Chen Y, Li X.* Characteristics of severe retinopathy of prematurity patients in China: a repeat of the first epidemic? Br J Ophthalmol 2006; 90(3): 268−71.
8. *Trinavarat A, Atchaneeyasakul LO, Udompunturak S.* Applicability of American and British criteria for screening of the retinopathy of prematurity in Thailand. Jpn J Ophthalmol 2004; 48(1): 50−3.
9. *Charan R, Dogra MR, Gupta A, Narang A.* The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol 1995; 43(3): 123−6.
10. *Varughese S, Jain S, Gupta N, Singh S, Tyagi V, Puliyel JM.* Magnitude of the problem of retinopathy of prematurity. experience in a large maternity unit with a medium size level-3 nursery. Indian J Ophthalmol 2001; 49(3): 187−8.
11. *Dutta S, Narang S, Narang A, Dogra M, Gupta A.* Risk factors of threshold retinopathy of prematurity. Indian Pediatr 2004; 41(7): 665−71.
12. *Oros A.* Retinopathy of prematurity. Belgrade: Zadudzbina Andrejevic; 2003.
13. *International Committee for the Classification of Retinopathy of Prematurity.* The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005; 123(7): 991−9.
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(12): 1684−94.
15. *Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A.* Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: ten year data from a tertiary care center in a developing country. Indian J Ophthalmol 2007; 55(5): 331−6.
16. *Shah PK, Narendran V, Saravanan VR, Raghuram A, Chattopadhyay A, Kashyap M,* et al. Fulminate retinopathy of prematurity - clinical characteristics and laser outcome. Indian J Ophthalmol 2005; 53(4): 261−5.
17. *Mihir Kothari M, Narendran V, Shah PK.* Ocular morbidity in premature children. [cited 2006 September 1]. Available from:http://www.pediatriconcall.com/fordoctor/diseasesandcondition/
18. *Vinekar A, Trese MT, Capone A Jr.* Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Cooperative Group. Evolution of retinal detachment in posterior retinopathy of prematurity: impact on treatment approach. Am J Ophthalmol 2008; 145(3): 548−555.
19. *Alme AM, Mulhern ML, Hejkal TW, Meza JL, Qiu F, Ingvoldstad DD,* et al. Outcome of retinopathy of prematurity patients following adoption of revised indications for treatment. BMC Ophthalmol 2008; 8: 23.
20. *O'Keefe M, Kirwan C.* Screening for retinopathy of prematurity. Early Hum Dev 2008; 84(2): 89−94.
21. *Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus.* Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2006; 117(2): 572−6.
22. *Cryotherapy for Retinopathy of Prematurity Cooperative Group.* Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years. Arch Ophthalmol 2001; 119(8): 1110−8.
23. *Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A.* Retinopathy of prematurity in middle-income countries. Lancet 1997; 350(9070): 12−4.
24. *Phan MH, Nguyen PN, Reynolds JD.* Incidence and severity of retinopathy of prematurity in Vietnam, a developing middle-income country. J Pediatr Ophthalmol Strabismus 2003; 40(4): 208−12.
25. *Fang PC, Kuo HK, Ko TY, Chen CC, Hwang KP, Chung MY.* Retinopathy of prematurity in larger preterm infants. Am J Perinatol 2006; 23(5): 273−7.
26. *Mathew MR, Fern AI, Hill R.* Retinopathy of prematurity: are we screening too many babies? Eye (Lond) 2002; 16(5): 538−42.

27. *Larsson E, Holmström G.* Screening for retinopathy of prematurity: evaluation and modification of guidelines. Br J Ophthalmol 2002; 86(12): 1399−402.
28. *Schalij-Delfos NE, Zijlmans BL, Wittebol-Post D, Tan KE, Cats BP.* Screening for retinopathy of prematurity: do former guidelines still apply? J Pediatr Ophthalmol Strabismus 1996; 33(1): 35−8.
29. *Ho SF, Mathew MR, Wykes W, Lavy T, Marshall T.* Retinopathy of prematurity: an optimum screening strategy. J AAPOS 2005; 9(6): 584−8.
30. *Lee SK, Normand C, McMillan D, Ohlsson A, Vincer M, Lyons C.* Evidence for changing guidelines for routine screening for retinopathy of prematurity. Arch Pediatr Adolesc Med 2001; 155(3): 387−95.
31. *Subhani M, Combs A, Weber P, Gerontis C, DeCristofaro JD.* Screening guidelines for retinopathy of prematurity: the need for revision in extremely low birth weight infants. Pediatrics 2001; 107(4): 656−9.
32. *Fortes Filho JB, Eckert GU, Procianoy L, Barros CK, Procianoy RS.* Incidence and risk factors for retinopathy of prematurity in very low and in extremely low birth weight infants in a unit-based approach in southern Brazil. Eye (Lond) 2009; 23(1): 25−30.

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