Screening for retinopathy of prematurity (ROP) in the middle Black Sea region of Turkey

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SUMMARY: Beden Ü, Demir S, Aygün C, Küçüködük Ş, Erkan D. Screening for retinopathy of prematurity (ROP) in the middle Black Sea region of Turkey. Turk J Pediatr 2012; 54: 223-229.

This study was designed to determine the frequency of retinopathy of prematurity (ROP) and the effectiveness of the screening protocol in preterm infants for our country. With these objectives, the charts of 1000 preterm infants were reviewed in Ondokuz Mayıs University, Department of Ophthalmology. ROP frequency, the effect of gestational age (GA) and birth weight (BW) and the effectiveness of the screening protocol were evaluated.

In this study, ROP was observed in 30.8% of infants and not observed in 69.2% of infants. Threshold ROP was detected in 7.0%. The frequency of threshold ROP was 43.5%, 20.0%, 12.6%, and 8.8% in the infants with GA of ≤26, 26–28, 29–30, and 31–32 weeks, respectively. Threshold ROP was not observed in babies born after 34 weeks. Treatment was required for 11% of the infants. ROP treatment requirement (11%) was limited to babies with GA of <34 weeks of gestation.

Incidence of ROP was inversely proportional with GA and BW. Treatment was not required when GA was >34 weeks. A new ROP screening protocol is proposed for Turkey, which is: screening of preterm babies with GA of <34 weeks and BW of <1800 g.

Key words: retinopathy of prematurity, screening protocol, prematurity, low birth weight, gestational age, multiple births.

Retinopathy of prematurity (ROP), originally known as "retrolental fibroplasia", is one of the leading causes of childhood blindness[1]. It is a vasoproliferative disease of the retina affecting preterm babies and is supposed to be mediated by vascular growth factors. Special risk groups include babies born with a birth weight (BW) of <1500 g and before the 32nd week of gestation[1]. The incidence of ROP reportedly differs between countries, with lower rates in developed countries and higher rates in developing or underdeveloped countries, where the survival of premature babies has increased, with limited monitoring of O_2 therapy[2]. In developed countries, embodying well-developed neonatal units, ROP is mainly a problem for babies with a BW of <1000 g. The results are different in developing countries, where more mature babies are also reported to develop ROP[3-5].

Regular screening is one of the most important determinants for effective management of babies with ROP. Screening allows the clinician to detect the disease at an optimum stage for treatment. The American Academy of Ophthalmology, American Academy of Pediatrics and American Association of Ophthalmology and Strabismus have recommended screening babies with a BW <1500 g or gestational age (GA) of ≤30 weeks and those babies who are considered at high risk by their attending pediatrician[6]. The threshold for ROP screening in the United Kingdom, however, is 1501 g for BW and 32 weeks for GA[1].

Many other countries are still trying to set their screening protocol, if they have not done so already. Defining the screening protocol is mandatory because it must be cost-effective, targeting those babies at most risk, and eliminating unnecessary examinations and clinical load. At the same time, it must be highly sensitive in order to not miss the babies with treatable disease, thus preventing permanent blindness. These protocols are in demand since

the ROP examination requires experienced ophthalmologists, which are reported to be declining in numbers because of time-consuming, poorly compensated examination methods and high rates of medico-legal suits relating to ROP screening[7]. As a result, the screening protocol is a kind of utility to achieve a balance between supply and demand for ROP screening. Today, different screening protocols should be considered more seriously for each country not only due to different ROP incidences in different countries, but also due to the fact that ethnicity was also detected recently as a risk factor, in addition to low BW and GA[8]. In the present study, we intended to assess the results of the ROP screening protocol in a tertiary ophthalmology clinic in Samsun, Turkey between 2003 and 2009.

Material and Methods

This is a retrospective chart review study conducted at Ondokuz Mayıs University, Ophthalmology Department, in accordance with the Helsinki Declaration. The records of 1000 babies who were screened for ROP between September 2003 and September 2009 were reviewed retrospectively. All babies born at or before the 34th gestational week or with a BW of <1800 g were screened. In developing countries, ROP screening may be different from that in developed countries, so we chose this criterion in our clinical practice. In addition, in the babies without these criteria, if the neonatologist decided that the baby was at high risk for ROP due to prolonged oxygen exposure, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, or mechanical ventilation, these babies were also examined for ROP. This protocol is applied as the screening criteria in order to detect as many threshold diseases as possible at the expense of high clinical load.

The parents were informed about ROP disease and the details of the ophthalmologic examination just after the baby arrived to the Neonatal Intensive Care Unit (NICU) and before the discharge of the baby from the NICU, according to the unit protocol by the attending neonatologist. Informed consent was obtained from the parents before the ophthalmological examination for ROP. The mother was told not to feed the baby for at least 60 minutes before pupillary dilatation. Pupillary dilatation was achieved by cyclopentolate 0.5% and phenylephrine 1%. Following pupillary dilatation, topical proparacaine hydrochloride 0.5% was instilled for a topical anesthesia, and patients were examined using a pediatric eyelid speculum. The anterior segment and pupillary examinations were performed by pen light, and the retinal examination was performed with an indirect ophthalmoscope employing +20 D fundus lens. Scleral depression was performed as necessary to see the peripheral retina. Topical antibiotic drops were applied to both eyes following examination for infection prophylaxis.

The ROP examination included assessment of pupillary dilatation, vitreous clarity, presence of plus disease, ROP stage, ROP location, and extent of the ROP disease. It was classified according to an International Classification of Retinopathy[9]. Ophthalmological examination results were recorded with respect to location of abnormal vasculature (Zone 1, 2, or 3), extent of the disease (by clock hours), severity (stage 1, 2, 3, 4, or 5), and presence (or not) of plus disease.

Treatment criteria were set according to revised indications for the treatment of ROP, which were derived from the results of the Early Treatment for Retinopathy of Prematurity Randomized Trial[10]. Based on these criteria, patients with type 1 ROP, defined as Zone 1, any stage ROP with plus disease, Zone 1, stage 3 ROP without plus disease, and Zone 2, stage 2 or 3 ROP with plus disease (to a lesser extent than that defined for threshold disease) were referred for treatment. A wait-and-watch policy was applied for type 2 ROP, defined as Zone 1, stage 1 or 2 ROP without plus disease, or Zone 2, stage 3 ROP without plus disease. Patients were referred for treatment immediately if threshold ROP was diagnosed. When type 1 disease was diagnosed, the patient was referred for treatment unless the parents refused the treatment and insisted on close follow-up for possible spontaneous regression of abnormal retinal vasculature. Prethreshold cases of type 2 ROP were followed with weekly ophthalmological examination if the parents were compliant with follow-up visits. If the parents were not eligible for frequent ophthalmological examination due to financial or accommodation problems, they were referred for treatment immediately.

Table I. Clinical Characteristics of Babies Included in the Study

	Singleton	Twins	Triplets	Quadruplets	Total
N	665	264	65	6	1000
Gestational age (weeks)	30.6 ±2.8	31.0 ±2.4	31.9 ±2.3	29.3 ±1.0	30.8 ±2.7
Birth weight (g)	1480 ±486	1492 ±360	1810 ±360	1101 ±228	1492±450
ROP (-) n (%)	462 (69.5%)	175 (66.3%)	52 (80.0%)	3 (50.0%)	692 (69.2%)
ROP (+) n (%)	196 (29.5%)	89 (33.7%)	13 (20.0%)	3 (50.0%)	308 (30.8%)
Mild ROP n (%)	111 (16.7%)	46 (17.4%)	7 (10.8%)	1 (16.7%)	165 (16.5%)
Type 2 n (%)	22 (3.3%)	7 (2.7%)	1 (1.5%)	0 (0%)	30 (3.0%)
Type 1 n (%)	26 (3.9%)	16 (6.1%)	1 (1.5%)	0 (0%)	43 (4.3%)
Threshold ROP n (%)	44 (6.6%)	20 (7.6%)	4 (6.2%)	2 (33.4%)	70 (7.0%)
Treated cases n (%)	68 (10.2%)	35 (13.3%)	5 (7.7%)	2 (33.4%)	110 (11.0%)

Values are given as average ± standard deviation.

The babies were grouped according to their GAs as: ≤26 weeks, 27–28 weeks, 29–30 weeks, 31–32 weeks, 33–34 weeks, 35–36 weeks, and ≥37 weeks. Babies were also grouped according to their BW as: ≤750 g, 751–1000 g, 1001–1250 g, 1251–1500 g, and >1501 g. Multiple births were also recorded. GAs, BWs, and multiple births of all babies were evaluated. The incidences of mild ROP, type 1 and 2 ROP, and threshold ROP for each group of BW and GA were calculated. Treatment requirement and time of treatment were among the other data assessed. The efficacy of the screening protocol was assessed and a convenient protocol was proposed for our area. Statistical analyses were performed using the SPSS 13.01, Statistical Package Program.

Results

Both eyes of 1000 infants (2000 eyes) were screened during the study period. The mean GA of all babies included in the study was 30.8 ±2.7 (24–38) weeks, and the mean BW was 1492± 450 g (590–3570 g).

Of the babies, 665 (66.5%) were singletons, 264 (26.4%) twins, 65 (6.5%) triplets, and 6 (0.6%) quadruplets.

Among the babies screened, 247 (24.7%) were born with GA of >32 weeks, and 76 (7.6%) were born with GA of >34 weeks. Among these 247 babies with GA of >32 weeks, 180 had a BW >1500 g. Moreover, among 76 babies with GA of >34 weeks, 53 had a BW >1800 g.

Retinopathy of prematurity (ROP) was detected in 308 (30.8%) of the babies: threshold ROP in 70 babies, type 1 ROP in 44 babies, type 2 ROP in 30 babies, and mild ROP in 164 babies. Treatment was required for 110 (11%) infants who were evaluated. Demographic characteristics of all cases and the incidence of ROP are presented in Table I.

Of the 1000 babies screened, 70 (7.0%) had threshold ROP, 44 (4.4%) had type 1 ROP and 30 (3.0%) had type 2 ROP. All the babies with threshold ROP (70 babies), 33 babies with type 1 ROP (75%), and 8 babies with type 2 ROP (26.6%) were referred for treatment. Hence, ROP regressed spontaneously in 11 babies with type 1 ROP (25%) and in 22 babies with type 2 ROP (73.3%). For 33 babies who had type 1 and type 2 ROP that regressed spontaneously, the average GA was 28.8±2.2 (25–35) weeks, and for 41 babies who were referred for treatment for type 1 or type 2 ROP, the average GA was 28.8±2.4 weeks (26–35). The difference was not statistically significant ($p>0.05$). When ROP regressed spontaneously in type 1 or 2 ROP, regression occurred in 45.2±3.1 (39–55) weeks of post-conception age.

Totally, 11% (110/1000) of babies were referred for treatment. The average GA of babies referred for treatment was 28.4±2.6 (24–34) weeks, and these babies were referred at an average post-conception age of 36.9±2.5 (32–44) weeks (nearly 8 weeks after birth).

Threshold ROP was diagnosed in 7.0% of all cases. The frequency of threshold ROP was 43.5%, 20.0%, 12.6%, and 8.8% in the infants whose GA was ≤26, 26–28, 29–30, and 31–32 weeks, respectively.

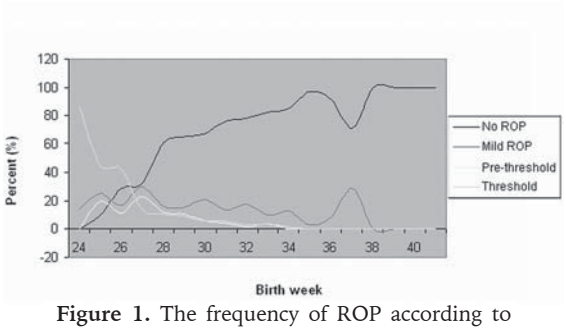

Figure 1. The frequency of ROP according to gestational age.

Among the babies with GA >32 weeks and BW >1500 g (n: 180), 21 babies were detected to have ROP (11.7%). Of these babies, 14 had mild ROP, 4 had threshold ROP, and 3 had type 1 ROP. Except for 14 babies with mild ROP, the other babies were referred for treatment (n: 7/180, 3.9%). Of these 7 babies, 6 were born at a GA of 33 weeks and 1 was born at 34 weeks. All these 7 babies referred for treatment had a BW >1500 g, and 3 had a BW >1800 g. When assessed for risk factors, of these 7 babies, 2 had sepsis and 1 had pneumonia. The other 4 babies did not have risk factors for ROP, which means that these 4 babies would have been missed if the screening criteria in the United Kingdom were applied. If the screening threshold was set at 33 weeks for GA, only 1 threshold ROP (with 34 weeks GA) and 9 mild ROP infants would have been missed. No threshold ROP, type 1 or type 2 ROP was observed in babies who were born after 34 weeks. However, 5 of these babies with mild ROP did not need treatment, and showed regression with regular follow-up (with GA of up to 37 weeks).

The frequency of ROP according to GA is shown in Figure 1. As can be seen in the figure, threshold ROP is very frequent in babies born before 26 weeks of GA, and the incidence decreases dramatically with every week of gestation. The frequency of threshold ROP was 80% in babies born at 24 weeks of gestation, whereas it was approximately 30% in babies born at 27 weeks of gestation. The frequency of threshold ROP declined gradually following 27 weeks of gestation, and no case of threshold ROP was observed in babies born after 34 weeks of gestation.

A detailed analysis of ROP according to GA is shown in Table II. Threshold ROP was diagnosed in 43.5% (27/62) of babies with GA ≤26 weeks, 7.6% (70/924) of babies with GA ≤34 weeks and in 7% (70/1000) of all cases that were screened during the study period. Of the 1000 babies screened, only 4 with GA >32 weeks were diagnosed as threshold ROP, and 3 were diagnosed as prethreshold type 1 ROP. The average GA of babies that were diagnosed as ROP was 29.4±2.7 (24–37) weeks, while it was 31.5±2.4 (25–38) weeks in babies without ROP. The difference was statistically significant ($p<0.001$).

The relationship between ROP and BW is presented in Figure 2. Similar to GA, the incidence of ROP was higher in babies with lower BW. The average BW of babies that were diagnosed as ROP was 1252±356 (590–2480) g, while it was 1595±447 (610–3570) g in babies without ROP. The difference was statistically significant ($p<0.001$).

There was no statistically significant correlation or difference between multiple births and the incidence and severity of ROP ($p>0.05$). Quadruplets were not included in the statistical analysis due to the small number of cases.

Discussion

Retinopathy of prematurity (ROP) is known to develop mainly in babies born at ≤32 weeks of GA and with BW <1500 g, though babies born later and heavier might also develop ROP with the presence of risk factors[4,5]. That explains why larger preterm babies exposed to long periods of oxygen/mechanical ventilation should also be screened for ROP.

The American Academy of Ophthalmology, American Academy of Pediatrics and American Association of Ophthalmology and Strabismus have recommended screening babies with a BW <1500 g or GA of ≤30 weeks and those

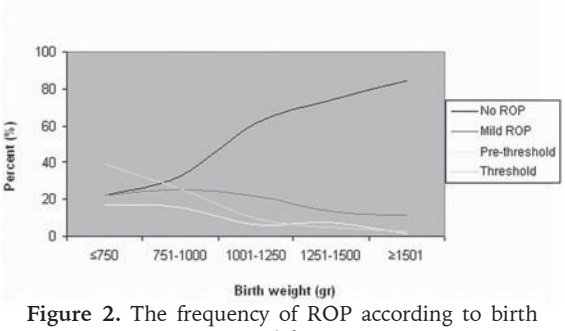

Figure 2. The frequency of ROP according to birth weight.

Table II. The Frequency of ROP According to Gestational Age

	n	Gestational Age (average ±SD)	Birth Weight (average± SD)	No ROP (n, %)	Mild ROP (n, %)	Type 2 ROP (n, %)	Type 1 ROP (n, %)	Threshold ROP (n, %)
All babies	1000	30.8±2.7	1492±450	692 (69.2%)	165 (16.5%)	30 (3.0%)	43 (4.3%)	70 (7.0%)
≤36 weeks	982	30.7±2.5	1475±429	676 (68.8%)	163 (16.6%)	30 (3.1%)	43 (4.4%)	70 (7.1%)
≤34 weeks	924	30.4±2.3	1440±396	621 (67.2%)	160 (17.3%)	30 (3.2%)	43 (4.7%)	70 (7.6%)
≤32 weeks	753	29.7±2.0	1368±365	478 (63.5%)	141 (18.7%)	28 (3.7%)	40 (5.3%)	66 (8.8%)
≤30 weeks	429	28.4±1.6	1202±292	234 (54.5%)	87 (20.3%)	22 (5.1%)	32 (7.5%)	54 (12.6%)
≤28 weeks	215	27.0±1.2	1088±283	93 (43.3%)	43 (20.0%)	15 (7.0%)	21 (9.8%)	43 (20.0%)
≤26 weeks	62	25.5±0.7	918±197	12 (19.4%)	12 (19.4%)	4 (6.5%)	7 (11.3%)	27 (43.5%)

babies who are considered at high risk by their attending pediatrician[6]. The threshold for ROP screening in the United Kingdom, however, is 1501 g for BW and 32 weeks for GA[11]. However, ROP screening criteria applied in high-income countries might not be appropriate for middle–low income countries. Recently, it has been suggested that each country should adopt its own screening criteria based on its own population results[12].

Retinopathy of prematurity (ROP) incidence can be higher in developing or underdeveloped countries where the survival of premature babies has increased, with limited monitoring of O_2 therapy. It has been reported in recent articles that more mature infants might develop ROP in such countries[2,4,13,14]. Binkhathlan et al.[2] reported that sensitivity of ROP screening is increased from 68% to 93% when the screening protocol is changed to involve babies with GA ≤34 weeks and BW ≤1800 g. Our study supports that result, since 7 out of 110 babies who were referred for treatment were above the threshold regarding both BW and GA. Similar to the results of Chen et al.[4] and Shah et al.[5], we also observed that 7 (2.8%) of the babies born at >32 weeks of GA developed prethreshold type 1 and threshold ROP that required treatment. Akman et al.[15] also recently suggested the screening in Turkey of preterm babies with GA of <34 weeks and BW of <1850 g, which is further supported by our data.

Among the proposed reasons for high ROP incidence in middle- or low-income countries are: poor O_2 monitoring, effect of ethnicity, or other undefined factors. Chow et al.[16] proposed that tighter control and monitoring of supplemental oxygen can reduce the incidence of severe ROP. A reduced O_2 protocol has also been detected to decrease the incidence of threshold ROP in infants[17,18]. The best level of oxygen supplement for premature infants is still under debate and is the subject of an ongoing study, the Benefits of Oxygen Saturation Targeting (BOOST) study (http://www.npeu.ox.ac.uk/boost).

Ethnicity is another factor proposed to be responsible for different ROP incidences in various countries. Aralikatti et al.[8] reported that Asian and black infants are more likely to develop ROP than white infants. A comparison

of their finding with the results of our study is not possible because the study was conducted in the United Kingdom, which renders the NICU standards different[11]. However, it can be considered that ethnicity may be another factor explaining why each country should have its own ROP screening criteria.

The reported frequency of ROP in Turkey varies between 24.2 to 46.7%[19-22]. In our study, 69.2% of all patients had no ROP of any stage, while 30.8% of babies had ROP of different stages. The results of our study, based on a larger population, are comparable with other reports from our country.

Treatment for ROP is advised in cases with type 1 prethreshold or threshold ROP. In the series by Larsson et al.[23], 11.5% of 513 preterm babies required treatment. Lad et al.[24] determined that laser photocoagulation was required in 7.7% of 27,435 preterm babies born in the United States from 1997–2002 and hospitalized more than 14 days. In a study from Iran, in which 953 babies were included, 34.5% of preterm babies were found to have ROP of different stages, and 16.5% of all cases necessitated treatment for ROP[25]. In a recent study from Turkey, including 318 babies with GA of ≤34 weeks, the incidence of any stage of ROP was 37.1%, and ROP treatment was needed in 16.1% of cases[26]. In a meta-analysis in our country by Ergenekon et al.[27], the frequency of advanced stage ROP was reported to be 9.3% in the population at risk. The data that was analyzed constituted approximately 2500 babies, and the frequency of ≥ stage 3 ROP varied between 0.7% and 24.7%. This is the largest series reported from Turkey. These findings are also paralleled by our study, in which total ROP incidence was detected as 30.8%, and the incidence of advanced ROP, which required treatment, was detected as 11%.

There is a strong correlation between BW and ROP; the incidence and severity of ROP increase as the BW decreases[11]. Choo et al.[28] stated that the requirement for therapy for ROP is increased two-fold in babies born weighing ≤750 g, when compared with those born at 751–1000 g. We also observed that babies with ROP are born approximately 300 g lighter than those without ROP, and the incidence of threshold ROP was highest in babies born weighing ≤751 g.

A correlation of GA with ROP has also been established. Austeng et al.[29] reported the incidence of ROP as 72.7% in 506 babies with GA ≤27 weeks (37.9% mild ROP and 34.8% severe ROP), and 19.6% required treatment. It is stated that GA is related to the development of ROP to a much greater extent than BW. In our study, 66.7% (122/215) of babies with GA ≤28 weeks were detected to have ROP. When we allocated babies included in this study according to their GA (Table II), 80.6% (50/62) of babies with GA of ≤26 weeks had ROP. This frequency decreased to 36.5% (275/753) for babies with GA of ≤32 weeks. We can emphasize with this graphic that for babies with GA <26-27 weeks, when GA decreases, the frequency of threshold ROP increases rapidly. For this reason, one should be more cautious while following babies with GA of ≤27 weeks and should frequently re-evaluate the babies in order to not miss treatable ROP.

The correlation between multiple order births and ROP is not obvious. Friling et al.[30] reported that in preterms with BW ≤1500 g, single birth was associated with a 2-3-fold increase in stage 2 and 3 ROP. In the present study, multiple births was not a risk factor for development of ROP.

In conclusion, of 1000 babies screened for ROP, the incidence and severity of ROP were highest in babies with GA of ≤26 weeks and BW of ≤750 g. In babies with GA ≤32 weeks, each two-week decrease in GA resulted in an approximately two-fold increase in the frequency of threshold ROP. Treatment for ROP was required in 11% of 1000 preterm babies. In this study, 7 infants that needed treatment would not have been detected if the ROP screening protocol accepted in developed countries (involving preterm babies with GA of <32 weeks and BW of <1500 g) had been used. Our data support that ROP cases that require treatment will not be missed if the screening protocol involves babies with a GA of ≤34 weeks and BW of ≤1800 g. Thus, we suggest that the screening protocol in our country involve preterm babies with GA of ≤34 weeks and BW of ≤1800 g for treatable ROP.

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