

# Retinopathy of prematurity: is it time to change screening limits in Lithuania?

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**Background:** National guidelines of screening for Retinopathy of prematurity in Lithuania were published in 1998. The upper limits were gestational age 35 weeks and / or birth weight 2500 g. The aim of the study was to determine the possibility of restricting the inclusion criteria for screening.

**Materials and methods:** The study cohort comprised 664 prematures of gestational age at birth  $\leq 35$  weeks and / or birth weight  $\leq 2500$  g, hospitalized to Vilnius University Children's Hospital in the period 1 of January 2000–31 of December 2002. Retinopathy of prematurity was found in 148 (22.3%) infants; 65 infants (9.8%) reached the threshold and underwent cryotherapy and / or laser therapy.

**Results:** All cases of threshold ROP were confined to infants with gestational age  $\leq 33$  weeks or birth weight  $\leq 1920$  g. Restricting the inclusion criteria for screening to  $\leq 1500$  g would only have reduced the total number of screenings and could have allowed us to miss 7 of our threshold cases. If ROP screening is limited to infants with GA of  $\leq 28$  weeks, 20 infants (30.8 %) would not have been screened and would not have been treated in 2000–2002 years.

**Conclusions:** Based on our results, it seems appropriate to include into the screening program all infants with gestational age  $\leq 33$  weeks and / or birth weight  $\leq 2000$  g. At the moment, the worldwide recommendations of screening for ROP are still not suitable in our country.

**Key words:** retinopathy of prematurity (ROP), screening, prevention of blindness, gestational age (GA), birth weight (BW), postconceptional age (PA), chronological age (CA)

## INTRODUCTION

Modern techniques of neonatal intensive care have resulted in increased survival rates among low birth weight infants. They are at the greatest risk of developing retinopathy of prematurity (ROP).

In Lithuania, the advancements in neonatology brought the “delayed” wave of ROP in the middle of the last decade. Introduction of binocular indirect ophthalmoscopy and the possibility to accept the International Classification of ROP, (1, 2) allowed us to start with the early and proper diagnosis of the disease and its treatment of it as well.

The national guidelines of screening for ROP in Lithuania were published in 1998 (3). The upper limits were GA 35 weeks and / or BW 2500 g. The aim of the study is to determine the possibility of restricting the inclusion criteria for screening.

## MATERIALS AND METHODS

A retrospective study of 664 infants with GA  $\leq 35$  weeks and / or BW  $\leq 2500$  g (limits of screening for ROP in Lithuania) born in Vilnius Perinatal Centre regions and admitted to the neonatal unit of Vilnius University Children's Hospital from January 1, 2000 till December 31, 2002 were screened for ROP. All infants were out born.

Children were excluded if they were born not in Vilnius county and were transferred to VUCH for ROP treatment only.

Phenylephrine 2.5% and Tropicamide 0.5% solutions were used for dilation of the pupils. An all-pupil binocular indirect ophthalmoscope (Keeler, England) and + 28 D lenses (Nikon, Japan) were used for examinations. Lid speculum was employed in all babies. The strabismus hook was used for rotation and indentation (if necessary) of the globe. The same two ophthalmologists, the authors of the paper, performed all examinations. Both specialists checked up the baby, if any stage of ROP was detected.

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Retinal vascular changes were recorded in accordance with the International Classification of ROP (1, 2).

Prior to the current study, one-year retrospective study by the same ophthalmologists published in 1998 (3) was carried out. It made possible to standardize the examination techniques and to draw basic guidelines for this study. On that ground to detect the earliest vascular changes for an infant born before week 29, the first examination was performed at the chronological age (CA) of 5 weeks, for babies born at 30–31 weeks at the age of 4 weeks, and for those born older than 32 gestation weeks at 3 weeks of CA. The subsequent examinations were performed with an interval of two weeks until the retina was fully vascularised. If ROP was detected, the control was intensified (once or twice a week).

For a more detailed investigation the infants were subdivided into subgroups by birth weight (BW) and gestational age (GA) according to Perinatal Audit (4) recommendations. Babies with birth weight <1000 g were included into the first subgroup of extremely low BW (ELBW). The second subgroup of very low BW (VLBW) comprised infants with birth weight 1000–1499 g. Into the third subgroup – low BW (LBW) – included were babies with birth weight  $\geq 1500$  g.

### Statistical evaluation

Analysis of data was performed using confidence intervals for factor means, standard error of mean (SEM) or standard deviation (SD). Significance level (p value) was counted using the two simple t test. The result was reported as significant if the p value was less than 0.05.

### RESULTS

During 2000–2002, ROP was documented in 148 (22.3%) out of 664 screened babies. The maximum stage of ROP was stage 1 in 29 (4.4%), stage 2 in 44 (6.6%) and stage III (less than threshold) in 10 (1.5%) out of babies screened for ROP. 65 babies (9.8%) had more than 5 contiguous or 8 cumulative clock hour involvements (threshold ROP) and underwent therapy for ROP. The birth weight of ROP infants ranged from 450 to 2300 g (mean  $\pm$  SD = 1246.1  $\pm$  377.3 g), and gestation age (GA) varied from 23 to 36 weeks (mean  $\pm$  SD = 28.7  $\pm$  2.5 weeks).

Table 1. Birth weight data of all screened infants

ROP level	Number of infants	BW, grams		
		Average	Stand. error	Median
No ROP	516	1925.3	18.1	1910
ROP < threshold	83	1368.7	41.4	1370
Threshold ROP	65	1089.6	39.8	1090
TOTAL	664	1773.9	19.1	1800

The mean BW was 1479.4  $\pm$  406.3 g for stage 1, 1328.2  $\pm$  357.3 g for stage 2, 1226  $\pm$  375.8 for stage 3 (less than threshold) and 1089.6  $\pm$  317.5 g for threshold infants. The difference between mean BW of ROP groups was statistically significant, except the mean BW of infants with stage 2 and stage 3 (less than threshold) ROP.

The mean GA at birth was 30.0  $\pm$  2.6 weeks for stage 1, 29.0  $\pm$  2.5 weeks for stage 2, 28.3  $\pm$  2.2 for stage 3 (less than threshold) and 27.9  $\pm$  2.3 weeks for threshold infants, the difference between the mean GA of ROP groups being also statistically significant, except mean GA of infants with stages 2 and 3 (less than threshold) ROP.

Table 1 presents BW and Table 2 GA data on all screened infants by ROP level.

There were 264 (51.2%) males and 252 (48.8%) females in the non-ROP group; 68 (45.9%) males and 80 (54.1%) females had some stage of ROP. The difference was statistically significant ( $\chi^2 = 1.25$ ,  $p < 0.01$ ).

The BW of non-ROP boys (mean  $\pm$  SD) was 1967.6  $\pm$  405.1 g, and BW of non-ROP girls was 1881.0  $\pm$  415.8 grams. The difference was statistically significant ( $p < 0.008$ ). The BW of ROP boys was 1333.9  $\pm$  370.8 grams and BW of ROP group girls was 1171.6  $\pm$  368.9 grams. The difference was statistically significant ( $p = 0.004$ ).

The distributions of non-ROP and ROP subgroups of infants in connection with their GA and BW are presented in Figs. 1 and 2.

The prevalence of ROP stage 3 (+) more than 5 contiguous or 8 cumulative hours involvement was found in 54.2% of eyes in the ELBW subgroup, in 24.2% of eyes in VLBW subgroup and in 1.4% of eyes in the LBW subgroup of screened infants (Table 3).

Threshold ROP was found in 53.4% of eyes in the first subgroup of GA, 14.4% of eyes of the second subgroup and 1.5% of eyes in the third subgroup of GA. 9.8% of total screened eyes developed threshold ROP (Table 4).

56.1% (83/148) of infants affected by ROP remitted spontaneously.

The mean postconceptional age (PA = GA + CA) of threshold ROP infants at the time of treatment was 36.4  $\pm$  0.3 weeks. Average (mean  $\pm$  SE) PA at cryo and / or laser therapy in the first subgroup of BW was 36.5  $\pm$  1.4 weeks, in the second 36.0  $\pm$  0.4 weeks and in the third subgroup 38  $\pm$  1.4 weeks. The differences in PA of all subgroups were not statistically significant.

Table 2. Gestational age and ROP level

ROP level	Number of infants	GA, weeks		
		Average	Stand. error	Median
No ROP	516	32.8	0.1	33
ROP < threshold	83	29.2	0.3	29
Threshold ROP	65	27.9	0.3	28
TOTAL	664	31.9	0.1	32

There was a significant positive correlation between gestation age and postconceptional age at treatment of threshold ROP (correlation coefficient 0.44), but no correlation was found between BW and PA at treatment (correlation coefficient 0.07). Linear regression analysis was performed to check if there were associations between BW, GA and PA at therapy (Figs. 3, 4). Only GA was associated with PA at therapy (F-ratio: 15.98,  $p = 0.0001$ ), BW was not associated with PA (F-ratio: 0.32,  $p = 0.6$ ).

Table 5 displays the number of threshold ROP infants that would not have been screened and would not have received therapy for ROP, following Worldwide Recommendations for Screening. We would have missed 2–3 threshold ROP prematures if we followed the world-

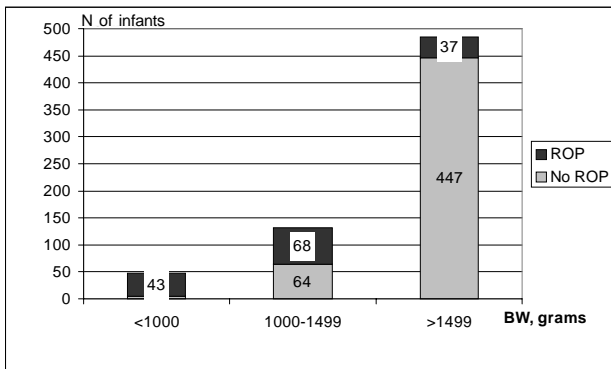


Fig. 1. Distribution of non-ROP and ROP infants by birth weight (BW)

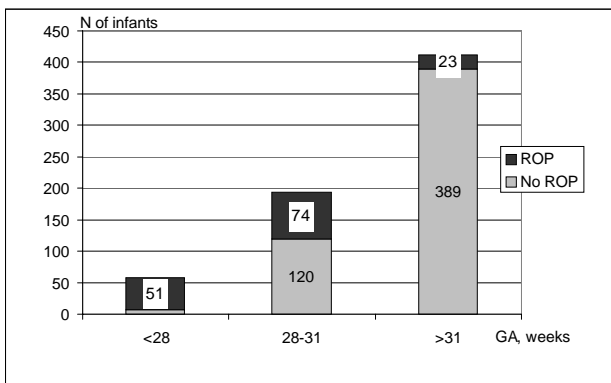


Fig. 2. Distribution of non-ROP and ROP infants by gestational age (GA)

Table 3. Relation of threshold ROP to birth weight

BW subgroups	ELBW	VLBW	LBW	Total
Threshold ROP,				
n of eyes (%)	52 (54.2)	64(24.4)	14(1.4)	130(9.8)
Total screened,	96	264	968	1328
n of eyes				

Table 4. Relation of threshold ROP to gestational age

GA, weeks	<28	28–31	>31	Total
Threshold ROP,				
n of eyes	62(53.4)	56(14.4)	12(1.5)	130(9.8)
Total screened,	116	388	824	1328
n of eyes				

wide 1993 recommendations for screening (see Table 6). If the AAOPS recommendations for screening were followed, we would have missed 16 infants by GA or 7 infants with threshold ROP by BW. It means that 24.6% of premature babies suffering from threshold ROP would not have received therapy.

DISCUSSION

A comprehensive screening program should be established that would ensure identification of affected infants. There are different screening recommendations in different countries of the world (5) (Table 6).

The leading one is from the Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO ROP CG) (6–8). The Joint Statement of the American Academy of Paediatrics, the American Association for Paediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology (9) outlines the principles upon which a screening program to detect ROP infants at risk might be based: infants with a birth weight of less than or equal to 1500 g or with gestational age of 28 weeks or less as well as infants weighing more than 1500 g with an unstable clinical course fell to be at high risk.

We would like to make some comments, derived from the results of our study, on the design of the screening program. We suggest that inclusion of children in a schedule cannot be based on gestational age only, at least in Lithuania where ultrasonography is routinely not performed in the

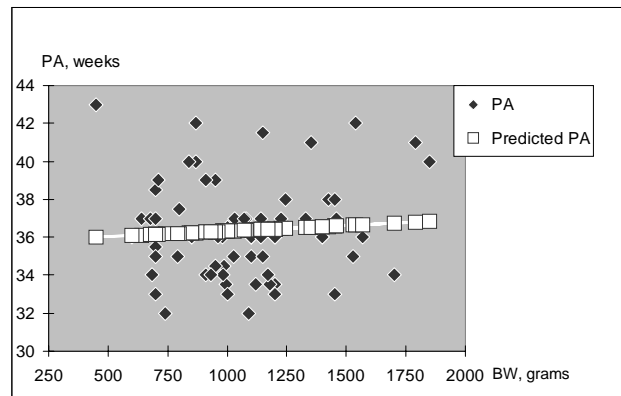


Fig. 3. Linear regression analysis of threshold infants by BW and PA at therapy

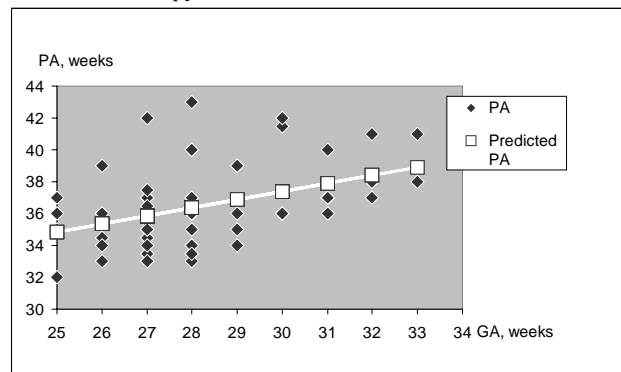


Fig. 4. Linear regression analysis of threshold infants by GA and PA at therapy

Table 5. Numbers of treated infants by GA and BW

GA, weeks	n of infants	BW, grams	n of infants
<26	8	<500	1
26	8	500–749	11
27	15	750–999	14
28	14	1000–1249	25
29	4	1250–1499	6
30	6	1500–1719	4
31	4	1750–1999	3
32	4	2000–2249	0
33	2		
34	0		

Table 6. ROP screening recommendations (worldwide, 1993)

Author	Country	GA (weeks)	BW (grams)
Lappl	Finland	28	1000
Schulenburg	United Kingdom	30	1500
WHO	-	31	1500
Cats	The Netherlands	32	-
Jacobson	Sweden	32	-
Holmstrom	Sweden	32	-
Maly	Sweden	32	1500
Clark	United Kingdom	32	1500
Fielder	United Kingdom	-	1700
Bech	Denmark	32	1750
Fledelius	Denmark	32	1750

(GA = gestational age, BW = birth weight, WHO = World Health Organisation).

first trimester of the pregnancy. All cases of threshold ROP were confined to infants with gestational age  $\leq$  33 weeks or birth weight  $\leq$  1920 g. No ROP more than stage 1–2 was observed in infants with gestational age  $\geq$  34 weeks or birth weight  $\geq$  2000 g. Restricting the inclusion criteria for screening to  $\leq$  1500 g would only have reduced the total number of screenings and could have allowed us to miss 7 of our threshold cases. If ROP screening is limited to infants with GA of  $\leq$  28 weeks, 20 infants would not have been screened and would not have been treated in 2000–2002. We therefore suggest inclusion of children with GA of 33 weeks or less and BW of 2000 grams or less into the screening program, at least in our area.

Our new screening limits would allow us to reduce the numbers of screening and exclude from screening 136 (20.5%) infants.

It is evident that screening limits are an ever changing factor. It depends on the achievements in neonatology. For example, in Sweden the screening limits were changed after 10 years. They overstepped the upper limit even less than we did: from 32 to 31 weeks of GA (10, 11). However, the progress in this field became much quicker in the last decade. During a very short period of time (since 1998, when our screening guidelines were established, till 2002, when

we accepted the new limits), we have made a remarkable step forward, cutting the screening limits for two weeks by GA and 500 grams by BW. We do believe that very similar events have happened in many developing countries.

## CONCLUSIONS

1. Infants with birth weight 2000 g or less and gestational age 33 weeks and less should be included into the screening program.

2. The worldwide recommendations of screening for ROP are not yet suitable in Vilnius County.

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