RETINOPATHY OF PREMATURITY (ROP)

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Abstract

ROP is a medical condition that may occur in the case of premature babies which, when left untreated, can lead to blindness. However it is a condition that can be successfully treated if it is discovered early enough. The incidence of the condition depends on the degree of prematurity, fetal factors (anemia/ blood transfusions, intraventricular hemorrhage, chronic pulmonary disease), maternal factors (Corioamniotitis, in vitro fertilization and obstetrical events) as well as the standard of neonatal care (the presence of oxygen blenders being essential).

Rezumat: Retinopatia de prematuritate

Retinopatia de prematuritate este o problema medicala ce apare la copiii nascuti prematuri care, netratata poate duce la cecitate. Cu toate acestea este o conditie care toate fi tratata cu success, daca este depistata in timp util. Gradul de incidenta depinde de gradul prematuritatii, factorii de risc fetali (anemia/ transfuzii sanguine, hemoragii intraventriculare, boala pulmonara cronica), factorii de risc materni (corioamniotita, fertilizare in vitro si evenimente obstetricale) cat si de nivelul ingrijirii neonatale.

Cuvinte cheie: Retinopatie de prematuritate, cecitate, factori de risc, screening

Introduction

ROP is a vasoproliferative retinopathy that affects premature babies, being the main cause of childhood blindness. ROP incidence is inversely proportional to birth weight (BW) and gestation age (GA).(1)

Normal vasculature

Retina is the only tissue that is avascular until 4th month of gestation. The retinal vessels develop centrifugally from the optic nerve, the hialoidian vessels being the starting point. The retinal vessels completely vascularize the nasal retina around 36 weeks of gestation and the temporal retina around 40 weeks (wks) (2) (figure 1).

Oxygen role in ROP

The immature and incompletely vascularized retina is sensitive to oxygen toxicity. This is one of the most important causes of ROP.

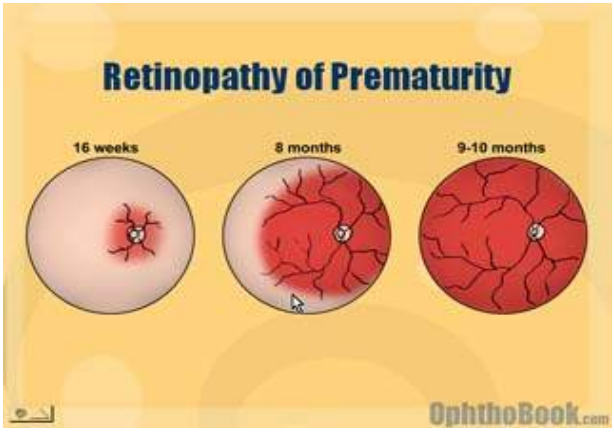

Fig. 1 Retinopathy of Prematurity(3)

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KEY WORDS: ROP, blindness, risk factors, screening

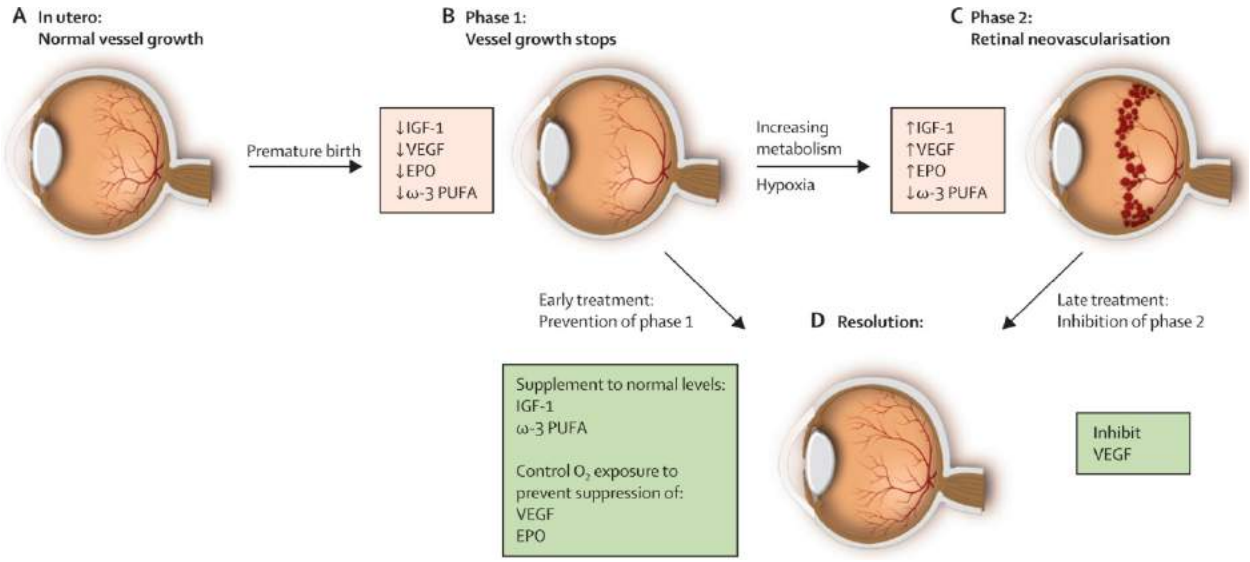

Fig.2 Progression of retinopathy of prematurity (6)

After birth, the hyperoxia of the surrounding environment as well as the supplemental oxygen, decrease the vascular endothelial growth factor (VEGF) and cease the retinal vessels development. Afterwards the retinal metabolic needs increase and, as a result, increase VEGF, that leads to the stimulation of retinal neovascularization; these new vessels can regress spontaneously or can lead to the retinal traction and retinal detachment if left untreated.(4,5) (Figure 2)

Pathogenesis

ROP is a disease that affects the vascular retinal development, being typical for premature babies. The normal retinal vascular development begins at 16 wks of gestation. The vessels start from the optic nerve and advance towards the retinal periphery. In the event of premature birth, the blood vessels could stop for a while, but, after *resuming the process of evolution,* the majority of babies succeed in having normal vessels. However, some babies develop abnormal neovascular tissue, that can proliferate, leading to bleeding and traction, and, without treatment, to total retinal detachment (4,7).

Classification:

By **location**. There are described 3 concentric zones of retina (Figure 3), which are centered on the optic disk:

Zone I - At the posterior pole, an imaginary circle with a radius equivalent to two times the distance from the optic nerve to the fovea

Zone II - The surface between the edge of the Zone I and a circle with the centre at the optic disk, tangent at the nasal ora serrata

Zone III – The residual crescent of the peripheral retina, anterior to Zone II. (2,8)

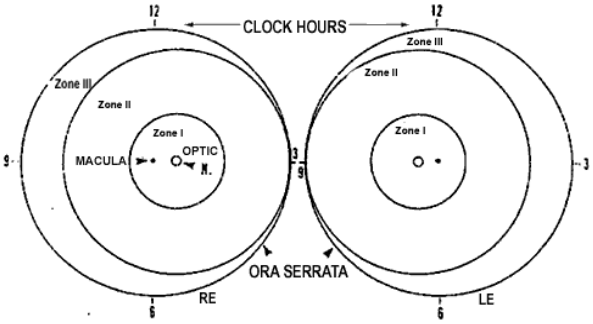

Fig. 3. ROP classification by location (9)

The Plus Factor: additional factor with increased venous dilatation and arteriolar tortuosity of the posterior pole. It can increase in severity, including by iris vessels engorgement, poor pupillary dilatation and vitreous haze.

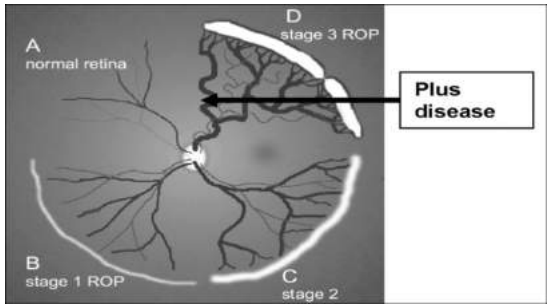

Fig. 4. ROP classification by severity (10)

ROP is classified in 5 stages, from the mild form (Stage 1) to most severe form (Stage 5):

Stage 1: A demarcation line between the vascularized and avascular retina (flat, white) Fig. 6. (11)

Stage 2: A ridge (prominent line, pink / white) (Fig. 7) (11)

Stage 3: Ridge with extraretinal fibrovascular proliferation (Fig. 8) (11)

Stage 4: Partial retinal detachment:

4A - Extrafoveal (Fig. 10) (11)

4B - Including the fovea (Fig.11) (11)

Stage 5: Total retinal detachment (Fig.12) (11). (5,8)

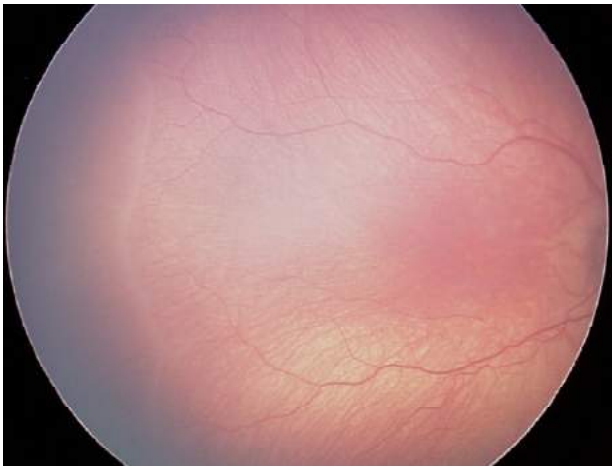

Fig. 5 The normal retina. (11)

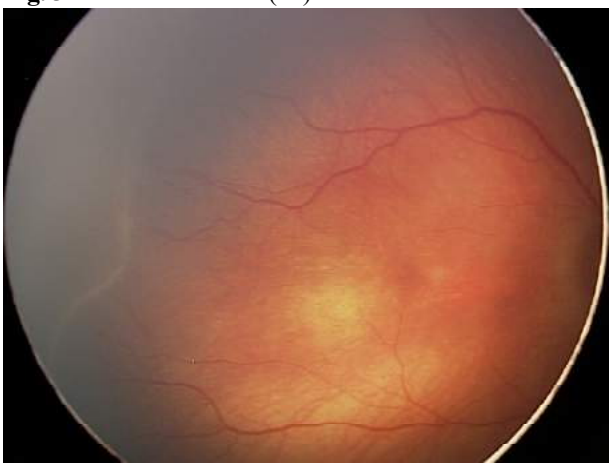

Fig. 6 Stage 1: A demarcation line between the vascularized and avascular retina (flat, white). (11)

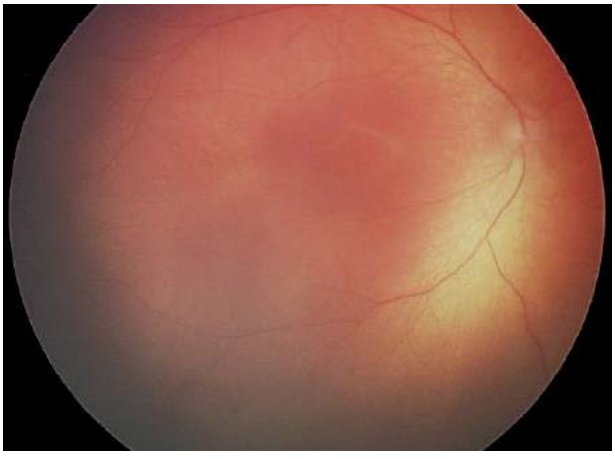

Fig. 7 Stage 2: A ridge (prominent line, pink / white) (11)

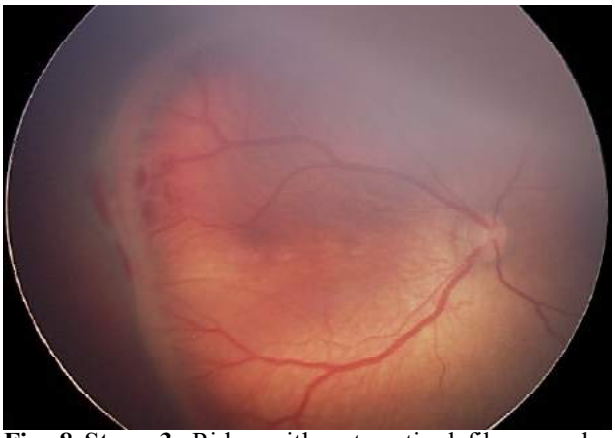

Fig. 8 Stage 3: Ridge with extraretinal fibrovascular proliferation (11)

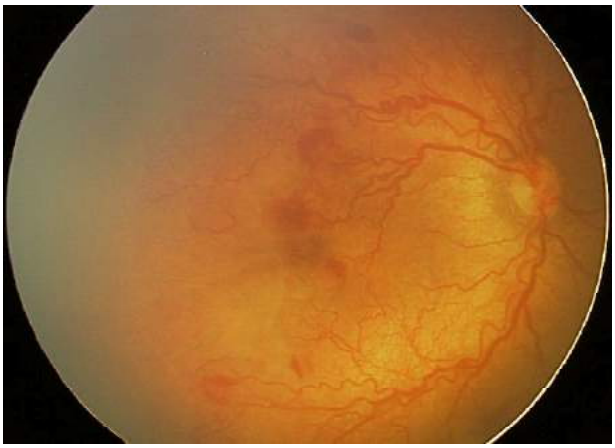

Fig. 9 Aggressive posterior ROP: Atypical ROP with blood vessels only in Zone I, without macular development, with severe plus factor

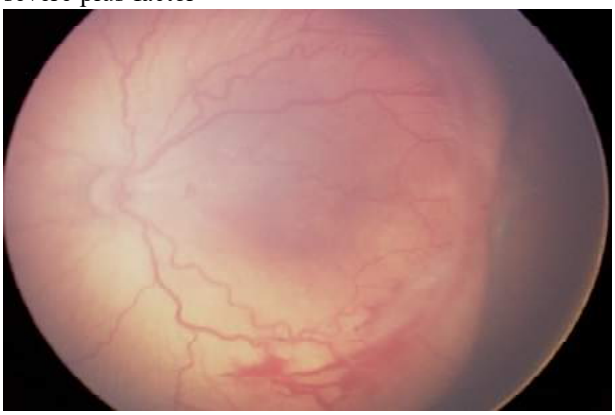

Fig. 10 4A - Extrafoveal (11)

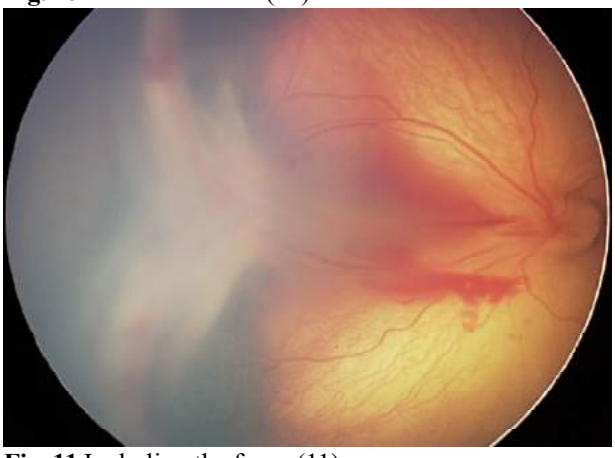

Fig. 11 Including the fovea (11)

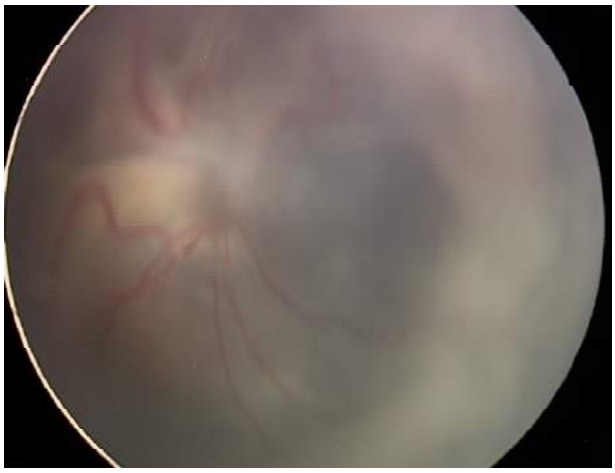

Fig. 12 Stage 5: Total retinal detachment (11). (5,8)

ROP risk factors:

In the literature, multiple interconnected intricate risk factors are mentioned such as: maternal, fetal and related to the perinatal care.

· Prematurity level: ROP incidence is higher for a higher prematurity level

· Peri- and postnatal risk factors:

- birth reanimation with 100% oxygen
- supplemental oxygen administration
- surfactant administration
- sepsis
- necrotizing enterocolitis (NEC)
- multiple blood transfusions
- intraventricular hemorrhage
- low postnatal weight gain
- delayed enteral nutrition
- unassisted delivery

· Maternal factors implied frequently in premature birth:

- preeclampsia and eclampsia
- chorioamnionitis
- diabetes mellitus
- obesity
- in vitro fertilization
- multiple pregnancies
- low educational and socio-economic status
- extreme maternal age

Screening

ROP undiagnosed and untreated in due time could lead to blindness for the entire life.

In Romania, since 2002, the National Program for ROP Screening and Treatment has been running. Now there are 10 ROP screening centers (Bucharest, Iasi, Cluj-Napoca, Targu-Mures, Brasov, Sibiu, Oradea, Timisoara, Craiova, Constanta), the national coordinator being The National Institute for Mother and Child Health "Alessandrescu-Rusescu", Bucharest.

The real screening, respectively the examination of all the premature babies born in a maternity, is done only in the level 3 maternities (except Suceava, Bacau, Galati); the babies born in these 3 centers mentioned above, together with those born in the 40 level 2 units are screened in the 10 ROP centers across the country, transported with the ambulance or brought by the parents. This phenomenon is uncontrolled, and could unfortunately lead to the omission of some babies from screening and to the ROP related blindness.

In accordance with the Romanian Protocol, screening is **obligatory for** all of the babies with **GA less or equal with 34 wks and/or BW less or equal with 2000gr**, as well as for the babies with higher GA if they had some risk factors such as: supplemental oxygen administration with FiO, > 40%, neonatal sepsis, NEC, anemia +/- blood transfusions, neonatal shock, dopamine or caffeine administration.

The first exam is done at 4 wks after birth, but not before 31 wks post menstrual age (Figure 13). The next controls are done at 1-2 weeks interval, depending on the disease's gravity, until spontaneous or post treatment regression. (12,13)

Treatment

The main goal of the ROP Program is timely identification of the babies who need treatment and treatment implementation in due time.

The treatment criteria are based on International Classification of ROP (ICROP) and on the results of The Early Treatment for ROP (ETROP) Study. Depending on the severity of the disease, the treatment is:

· Laser therapy – the "Gold Standard" (for Treshold / Pretreshold ROP: stage 3 plus zone II /II

TIMING OF FIRST EYE EXAMINATION BASED ON GESTATIONAL AGE AT BIRTH

GESTATIONAL AGE AT BIRTH (wk)	AGE AT INITIAL EXAMINATION (wk)	
	Postmenstrual	Chronologic
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

Fig. 13. Timing of first eye examination (14)

posterior on 5 contiguous hours / 8 discontinuous hours)

·Intravitral Bevacizumab (Avastin) – for severe cases (AP-ROP, stage 3 plus ROP zone I/II posterior) or for zone II ROP to unstable infants, its advantage being that allows vascularization towards periphery with immediate effect and no visual loss.

· Vitreoretinal surgery (centers outside Romania) – for stage 4/5 (retinal detachment). (Fig14)

Prevention

I. **Primary prevention,** through a better ante-, peri- and postnatal care:

1. Respect of the regionalization of the maternities, thus all of the babies who have at birth GA less than 32 wks and/or BW less than 1500gr to be born or transferred in the level 3 units, where they have all care facilities and where the ROP screening is done in a complete procedure

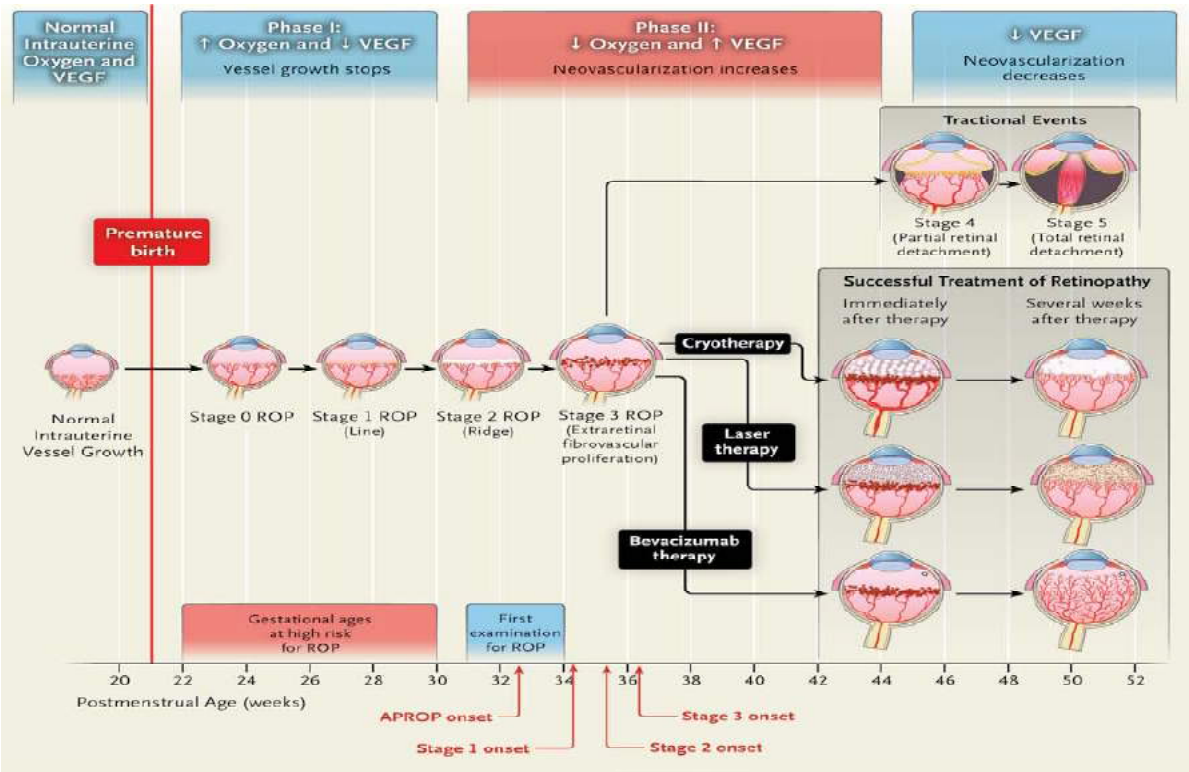

Fig. 14 Pathogenesis and Therapy of Retinopathy of Prematurity (ROP).(15)

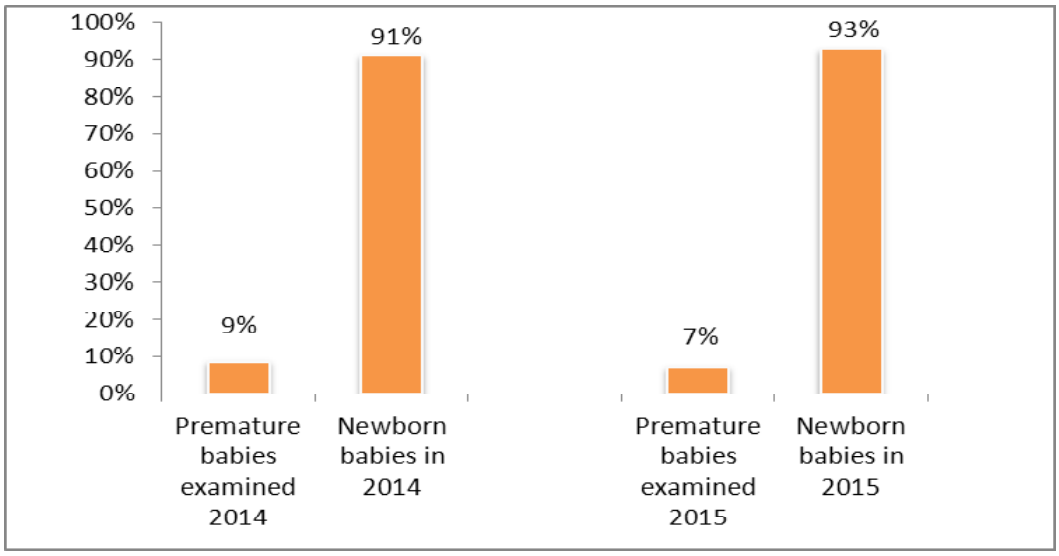

Fig. 15. Incidence of prematures births out of total

2. Strict adherence to the protocol of neonatal care and supplemental oxygen administration: Sa O, between 88-92% with care for avoiding higher fluctuations;

3. Standardization of neonatal care: early treatment and reducing the frequency of neonatal sepsis, early enteral nutrition, adequate parenteral nutrition, regular, scheduled staff education;

4. Antenatal care:

- Antenatal steroid administration at the pregnancies with GA between 24 and 34 wks when the birth is not impending, the effect being decreasing the frequency of newborn respiratory distress, the supplemental oxygen administration, the mechanical ventilation, the intraventricular hemorrhage, the NEC, the neonatal sepsis and demise;

- Precocious diagnosis and treatment for chorioamnionitis and puerperal sepsis for avoiding fetal affectation. (14)

II. **Secondary prevention,** thru performing ROP screening for all the babies in the group risk to benefit from treatment in due time. (12,13)

Material and method

The study has included 493 premature babies evaluated for ROP screening. The babies were born between January 2014 and December 2015 at the Neonatology Department of "Gheorghe Polizu" Clinic Hospital.

Results and considerations

Of the 493 premature babies examined, 60 had their retina vascularized already at the first control, 280 babies had immature retina (without ROP), 99 developed stage 1 ROP, 24 stage 2 ROP, 21 stage 3 ROP and 9 premature babies developed an especially aggressive condition. A total of 31 babies needed treatment as follows: 20 of them needed laser treatment, 9 needed treatment with intravitreous bevacizumab injection while 2 of them needed a combined treatment of both laser therapy and intravitreous bevacizumab.

The study was undertaken over a two year period during the 2014-2015 timeframe.

In 2014 the total number of newborn babies registered with the Neonatology Department of "Gheorghe Polizu" Clinic Hospital (births and transfers) was 3,231 out of which 259 premature babies that were examined as part of the National ROP Screening Programe, a share of 9% of the total number;

In 2015 the total number of newborn babies registered was 3,243 out of which 234 premature babies that were examined as part of the National ROP Screening Programe, a share of 7% of the total number. (Figure 15)

Out of the total 493 premature babies examined between January 2014 and December 2015, 457 had a gestation age lower than or equal to 34 weeks and 397 babies had a birth weight lower than

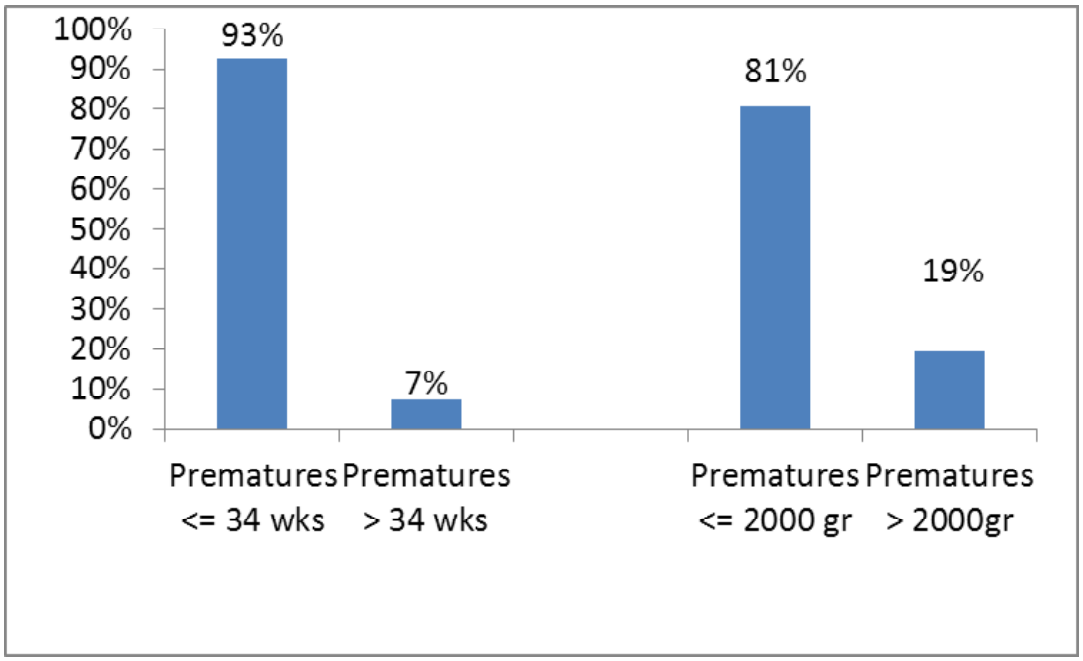

Fig. 16. Age and weight distribution of prematures babies

or equal to 2000 grams. (Figure 16). A total of 6 deaths occurred.

The split by condition severity among the 493 children examined is as follows (Figure 17):

340 (69%) babies without ROP

99 (20%) babies with stage 1 ROP

24 (5%) babies with stage 2 ROP

21 (4,2%) babies with stage 3 ROP

9 (1,8%) babies with aggressive form posterior condition

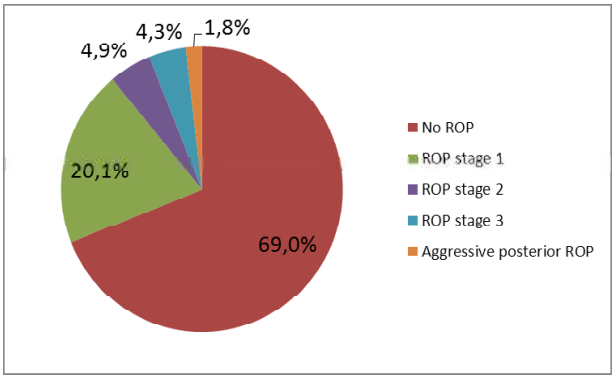

Fig. 17. Split by condition severity

Only 31 babies needed treatment, a share of 6.5% of the total, the types of treatment (Figure 18) were as follows:

20 (4%) prematures – Laser therapy

9 (2%) prematures – injection of Bevacizumab

2 (0,5%) prematures - both Bevacizumab and Laser therapy

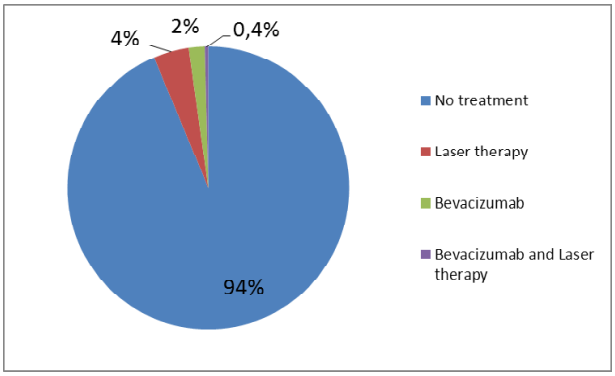

Fig. 18 Split by type of treatment from total

Within the study group, the determinants of the disease were more clearly seen in the group that also needed treatment. The main ones were: anemia/ sanguine transfusions, intraventricular hemoragies (IH), chronic pulmonary disease. (Table 2)

The maternal pathologies within the treated group are linked to the reasons for premature birth. The most common ones are: chorioamnionitis, in vitro fertilization and obstetrical events. (Table 1)

Table 1 Maternal pathologies

Mathernal pathologies within the treated group	
Placenta praevia	3
Corioamnionitis	5
Surgical Intervention	2
In vitro fertilization	4
Umbilical cord around neck	3
Treatment by dexamethazone	11
Obstetrical events	4

Table 2. Premature Pathologies

Premature pathologies within the treated group	
Transfontanellar ultrasound IH	23
Transfontanellar ultrasound Hidrocefalia	3
Chronic pulmonary disease	11
Anemia/ Sanguine transfusions (between 1 and 17)	30

Comparing patients treated in two different units, namely Unit 1 representing the children treated originating from Polizu maternity and Unit 2 representing children origination from level 2 maternities in Romania, we have the following results:

Table 3. Split of patient numbers by weight at birth between the 2 Units

Weight at birth	<= 1000g.	1001 – 1500g.	>= 1501g.
Unit 1	12	16	3
Unit 2	3	16	8

Judging by weight at birth, the number of the babies that needed treatment is equal in the 1001-1500 grams category irrespective of originating unit. In the category below 1000 grams the number of patients origination from Unit 1 is far larger than those originating in Unit 2. The situation is inverted for prematures in the category exceeding 1500 grams at birth. This reflects differences in the treatment standards closely linked to the different equipments available across Romania. The most visible example is the availability of oxygen blenders at all level 3 units while these equipments are unavailable at any level 2 units. (Table 3)

Table 4. Split of patient numbers by gestation age between the 2Units

Gestation Age	<= 26Wks	27-31Wks	>= 31Wks
Unit 1	9	16	6
Unit 2	2	13	12

Table 4 above shows a greater number of pacients needing treatment at higher gestation age among the set originating from Unit 2 (level 2 units) than the ones originating from Unit 1. The causes are also linked to the unavailability of equipments in these units as discussed previously.

Conclusions

1. Screening for ROP is a necessity for all premature babies from the risk group. When performed in a timely manner this prevents complications and loss of sight via ROP.

2. Risk factors mentioned in the specialty literature are also found in the researched set: chorioamniotitis and in vitro fertilization are among the first maternal pathologies that cause premature births below 34 weeks of gestation.

3.The association of ROP with intraventricular hemoragies (IH), hydrocephalus, BPC and multiple transfusions reflects the complex pathology that these premature babies have as well as the extended hospital stay and invasive therapies.

4. A particular aspect is represented by the large number of transfusions carried out. The further understanding of the anemies' etiology that called for the transfusions is highly necessary.

5. The analysis of the two groups from different maternities reflects differences in medical care due to different availability of equipments. A rise in number of premature babies below 1000 grams and with gestation age below 26 weeks is visible.

6. We should also note that 13% of treated premature babies originated from in vitro fertilization procedures and that only 38.6% received maternal prophylaxis with Dexametazone.

7. Chronic pulmonary disease (CPD) was present in 38.6% of the premature babies treated. Their oxygen-intensive therapy was an important risk factor for ROP.

8. Prophylaxis, screening and therapy by the obstetrician-neonatologist-ophthalmologist team lead to significant reduction of ROP especially when special medical assistance with adequate equipments is undertaken on a category of premature babies displaying multiple risk factors for long term pathology.

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