Journal of Medicine in Scientific Research

Volume 1 | Issue 3 Article 1

Subject Area:

Retinopathy of prematurity: A major review and situation analysis in Egypt

Ihab S. Othman
Cairo University, ihabsaad@hotmail.com

Recommended Citation

Othman, Ihab S. (2018) "Retinopathy of prematurity: A major review and situation analysis in Egypt," *Journal of Medicine in Scientific Research*: Vol. 1: Iss. 3, Article 1.
DOI: https://doi.org/10.4103/JMISR.JMISR_37_18

Review Article

Retinopathy of prematurity: A major review and situation analysis in Egypt

Ihab S. Othman[a,b]

[a]Department of Ophthalmology, Kasr Al-Aini University Hospital, Cairo University, [b]The Retina and Oncology Service, National Eye Center, Rod El-Farag, Cairo, Egypt

Abstract

Retinopathy of prematurity (ROP) remains a major cause of childhood blindness in developing countries. As childhood and neonatal mortality in Egypt has shown tremendous improvement over the past two decades, it is expected to encounter an increasing number of cases of blindness from ROP in surviving infants unless strict guidelines and cooperation between different involved departments are explicitly set. In this review article, the author highlights the studies conducted and published risk factors, recommends protocols for early diagnosis, and describes management strategies to lessen or prevent blindness related to ROP.

Keywords: Antivascular endothelial growth factor, developing countries, Egypt, laser, retinopathy of prematurity, surgery for stage 4 and 5

Introduction

Retinopathy of prematurity (ROP) represents a significant cause of preventable blindness for children in the developing and developed countries with the improvement of neonatal care. Several countries have adopted screening protocols for early detection and management of preterm infants having this potentially blinding disease. However, research on this issue in Egypt is still in its early stage [1].

Situation in Egypt

Owing to significant efforts of the health system in Egypt, infant mortality has declined from 40/1000 live births in the period from 1994 to 1998 to 22/1000 live births in 2014 [2]. The estimated number of premature births in Egypt in 2008 was 123 131 [3].

Survival of premature infants in Egypt has increased in the past few years owing to the advances in medical measures taken in the Egyptian neonatal intensive care units (NICUs). Neonatal mortality has dropped from 24 deaths/1000 live births in 2000 to 14 deaths/1000 live birth in 2014 [2,4]. The improvement in neonatal mortality rates reflects the increased standard of care of critically ill neonates in NICUs, as well as the increased possibility of ROP occurrence among other comorbidities. Screening of premature infants is essential to minimize blindness and long-term visual morbidity in these infants. More efforts need to be made not only to reduce the incidence of ROP but also to improve the guidelines to ensure that all babies at risk receive a timely screening examination.

The cost of screening and managing an infant is much lower than the lost productivity cost on the state exchequer. A child having gone blind because of ROP will remain so for 71.3 years (the life expectancy in Egypt, 2015; *http://www.who.int/countries/egy/en/*).

The economic burden of ROP is tremendous. A simple calculation incurs a monthly medication and care and productivity loss mounting to 8000 LE/month. The simple calculation for 70 years of life expectancy would be around 6 720 000 LE or 384 000 USD. If we consider inflation rates, national productivity changes, demographic changes, gross domestic product (GDP), and currency value changes, the numbers become unimaginable. The average cost of treatment of treatable ROP in early stages is a laser procedure or a simple intravitreal injection of antivascular endothelial growth factors (anti-VEGF) under general anesthesia mounting to

Correspondence to: Ihab S. Othman, FRCS (Glasg), 12 Mosaddaq Street, Giza, Egypt, Tel: +20 237 627 771/+20 100 176 8768. E-mail: ihabsaad@hotmail.com

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/JMISR.JMISR_37_18

How to cite this article: Othman IS. Retinopathy of prematurity: A major review and situation analysis in Egypt. J Med Sci Res 2018;1:136-44.

an average of 8000 LE and for late stages presenting with vitrectomy to 25 000 LE. Cost-benefit analysis suggests prompt treatment regardless of the cost. These simple figures demonstrate clearly that timely treatment of ROP is both efficacious and economically desirable. Because of the high lifetime costs of severe visual impairment, the early treatment strategy provides long-term cost savings [5].

The WHO global action plan on universal eye health

The average prevalence of blindness in countries ranges from 0.5 to 1.5%, with Afghanistan, Egypt, Djibouti, Somalia, and Yemen having the highest prevalence. The WHO global action plan on universal eye health from 2014 to 2019 aims to support efforts by member states to achieve a measurable reduction of 25% (compared with 2010) of avoidable visual impairment by 2019, with a particular focus on developing national action plans in line with the WHO framework for action for strengthening health systems. WHO global action plan targets ROP as a significant cause of preventable blindness in developing countries (*http://www.emro.who.int/annual-report/2016/health-promotion.html*).

Pathogenesis of retinopathy of prematurity

Retinal vascularization is initiated at 15–18 weeks of gestation (WG) (Fig. 1). Retinal blood vessels extend out from the optic disc, and grow peripherally to reach the ora serrata nasally at ~32–36 WG and temporally by 36–WG [7].

Human retinal vascular development occurs in two phases:

(1) Vasculogenesis: it is the de-novo formation of blood vessels from endothelial precursor cells. Vascular precursor spindle cells migrate along the distribution of the future major retinal blood vessels nasally and temporally to the optic disc forming the four major arcades in the posterior retina but do not migrate to the retinal periphery or the foveal zone [8].

(2) Angiogenesis: it is the development of new vessels by budding from already existing blood vessels. It increases capillary density at the central part of the retina and forming the peripheral vessels of the superficial and deep capillary plexus [8]. Angiogenesis starts after completion of vasculogenesis and terminates when the superficial and deeper retinal plexus have reached the ora serrata [9].

Pathogenesis of ROP: is postulated to consist of two distinct phases:

(1) Phase I: it is characterized by cessation of normal retinal vascular growth owing to loss of VEGF responsible for its development that are normally provided by the mother in utero during the third trimester of pregnancy. The relative hyperoxia caused by supplemental oxygen given to premature infants also downregulates VEGF.

This shift leads to stoppage of normal retinal vascular growth and vaso-obliteration of retinal vessels, leaving avascular retina in the periphery. The younger the preterm infant, the larger is the avascular area.

With the maturation of retina after birth, it becomes more metabolically active; therefore, the avascular retina becomes hypoxic, and then phase II develops [10].

(2) Phase II: hypoxia results in retinal neovascularization owing to the release of VEGF and other angiogenic factors, producing new vessels at the junction between vascular and avascular retina (arteriovenous shunts, Fig. 2) [11]. The new vessels are dilated, tortuous and leaky into the vitreous, followed by vitreous hemorrhage and even tractional retinal detachment [12].

IGF-1 is a nonoxygen regulated factor provided in utero through the placenta and amniotic fluid and is critical to normal retinal vascular development through the control of VEGF activation. After birth, IGF-1 level decreases. Its lack in the early neonatal period is associated with lack of vascular growth and with subsequent proliferative ROP. At 4-week postnatal age, VEGF and IGF-1 serum levels in premature infants can be used as indicators in ROP screening. Serum VEGF helps to predict the probability of suffering from the illness [13,14].

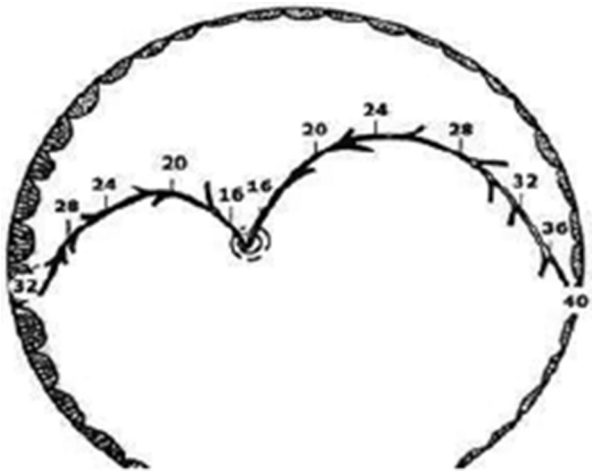

Figure 1: Diagram of retinal blood vessel development in humans. The numbers in the figure are weeks of gestation [6].

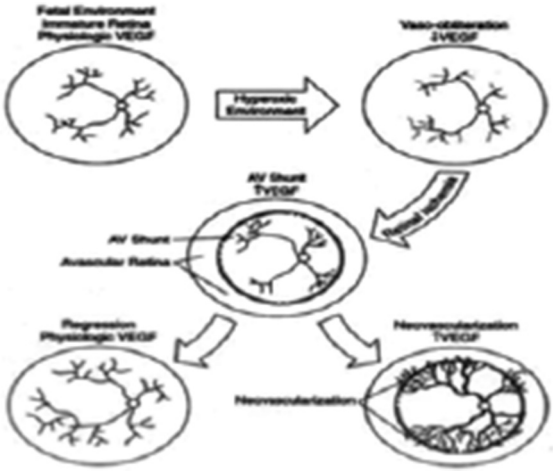

Figure 2: VEGF model of pathophysiology of ROP [11]. ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor.

Regression takes place when VEGF stimulates normal vascularization into the avascular retina [13,14].

Risk factors of retinopathy of prematurity in Egypt

In a large study of 402 preterm babies from neonatal ICUs in Mansoura city from March 2013 to March 2015, 237 (59%) cases had ROP, among whom 101 (42.6%) had stage 1, 114 (48.1%) had stage 2, 12 (5.1%) had stage 3, 10 (4.2%) had aggressive posterior retinopathy, and 24 (10.1%) presented with plus disease.

ROP occurred in 59% of all screened preterm babies. The main risk factors for the development of ROP were gestational age (GA), birth weight (BW), oxygen therapy, sepsis, multiple birth, and cesarean section [15].

Gilbert *et al.* [16] found that the younger the GA, the higher the incidence, and the more severe the disease. ROP is considered a disease of very premature infants in highly developed countries, but in middle-income and developing countries, more mature and larger babies remain at risk [15,16].

Low birth weight is a significant risk factor for ROP. Lermann *et al*. [17] proved that ROP development was inversely proportional to BW.

It is well documented that very low BW infants with fluctuating partial arterial oxygen pressure (PaO_2) are at higher risk of threshold ROP. Moreover, the duration of oxygen exposure is considered an important risk factor for the occurrence of the disease [18,19].

The supplemental therapeutic oxygen for threshold ROP (STOP-ROP) multicenter trial conducted a study to determine the efficacy and safety of supplemental therapeutic oxygen for infants. STOP-ROP concluded that use of supplemental oxygen did not cause additional progression of prethreshold ROP but also did not significantly reduce the number of infants requiring peripheral ablative surgery. However, it increased the risk of pneumonia and aggravated the chronic lung disease [20].

Other risk factors include infant characteristics like race, multiparity, and poor postnatal weight gain [21]; markers of severe illness including blood transfusion volume and iron load [22]; high doses of recombinant human erythropoietin [23]; surfactant therapy as it facilitates survival of high-risk preterm infants [24]; respiratory distress syndrome [25]; early initiation of total parenteral nutrition using multipurpose 10% lipid vials [26]; sepsis [27]; and indomethacin (NSAID) use in the treatment of patent ductus arteriosus [28].

Clinical features of retinopathy of prematurity

The International Classification of Retinopathy of Prematurity (ICROP) was developed to describe ROP using retinal landmarks and classify it according to several parameters: zone, extent, stage, and presence or absence of plus disease. The original ICROP described ROP first in 1984, expanded it in 1987, and clarified more on it in 2005.

The classification was according to zones centered on the optic nerve (Fig. 3), where zone 1 indicates more severe disease. Stages from 1 to 5 (Figs. 4 and 5) denote the abnormal vascular response at the junction of the vascular and avascular retina, and clock hours denote the extent of the disease over the retinal surface [29,30]. Plus disease (Fig. 6) indicates vascular incompetence mostly followed by rapid progression of ROP to retinal detachment and refers to venous dilation and arteriolar tortuosity of the vasculature in the posterior pole of the retina in at least two quadrants of the eye (usually ≥6 clock hour segment), vitreous haze, engorgement of the iris vessels, and poor dilation of the pupil.

A threshold ROP is defined as five contiguous clock hours or eight cumulative clock hours of stage 3 with 'plus disease' in the zone I or II (Fig. 7) [30]. This was an indication for prompt laser ablation to the peripheral ischemic retina.

Aggressive posterior retinopathy of prematurity

AP-ROP is considered as rapidly progressing. It is a severe form of ROP characterized by its posterior location, prominence of plus disease, and the ill-defined nature of the retinopathy (Fig. 8). It is observed most commonly in the zone I, but may also occur posteriorly in zone II. Early in AP-ROP, there is more dilation and tortuosity of the posterior pole vessels in all four quadrants out of proportion to the peripheral retinopathy. It advances rapidly and may progress to retinal detachment if left untreated.

Prethreshold retinopathy of prematurity

In 2003, a study described ROP as prethreshold and divided it into high risk (type 1) and low risk (type 2) based on the occurrence of an unfavorable outcome (Table 1) [31].

These unfavorable retinal outcomes include the following:

(1) Stage 4B, retinoschisis, or fold including fovea.
(2) Stage 5, total retinoschisis, or retrolental membrane blocking the visual axis.

Eyes are indicated for treatment when type I is present, but those with type II are still at risk for further progression and need close observation.

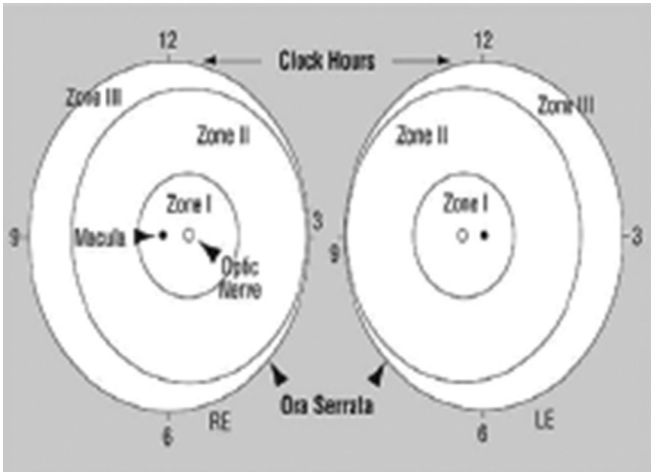

Figure 3: Scheme of the retina of the right eye (RE) and left eye (LE) showing zones and extent of ROP. All zones are centered around the optic nerve. Zone I: radius twice the distance from the optical nerve to the fovea [29]. ROP, retinopathy of prematurity.

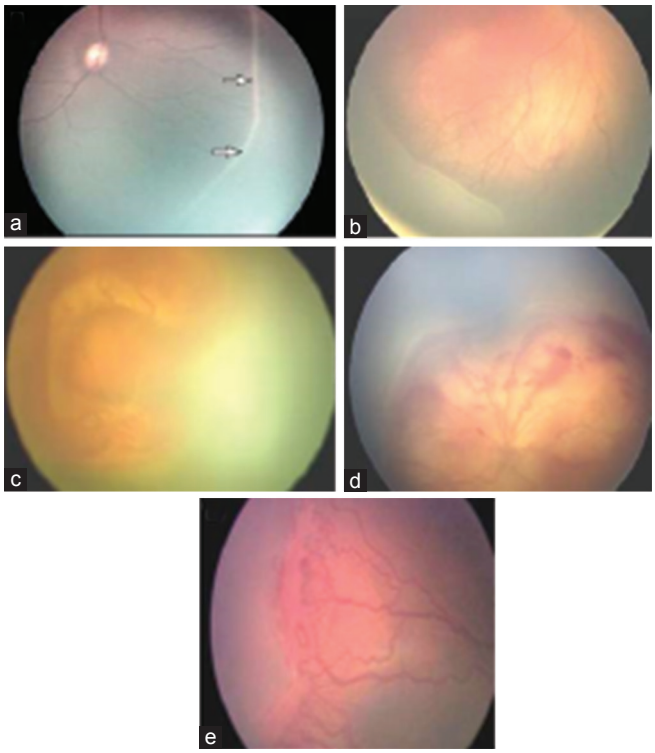

Figure 4: (a-d) and e show stage 1 (demarcation line), 2 (demarcation ridge), 3 (extra retinal fibro vascular proliferation), 4a (partial retinal detachment excluding the fovea), and 4b (partial retinal detachment including the fovea) ROP, respectively [29]. ROP, retinopathy of prematurity.

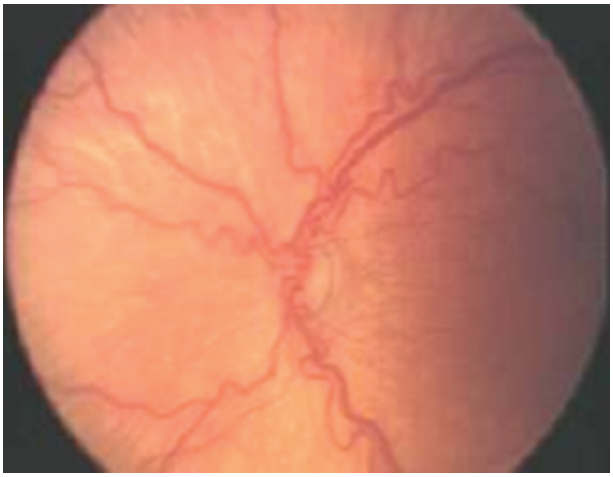

Figure 6: Plus disease [29].

Table 1: Prethreshold classification used for ETROP study [31]

Type 1: ROP 'high risk'	Type 2: ROP 'low risk'
Zone I: stage 1 or 2 with plus disease. Stage 3 with or without plus disease	Zone I: stage 1 or 2 without plus disease
Zone II: stage 2 or 3 with plus disease	Zone II: stage 3 without plus disease

ROP, retinopathy of prematurity.

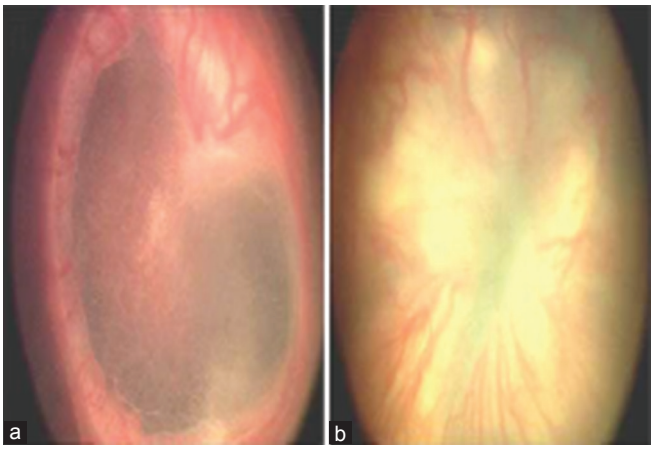

Figure 5: Stage 5 ROP. (a) Total retinal detachment with open funnel configuration. (b) Funnel retinal detachment that is opened anteriorly but narrowed posteriorly [29]. ROP, retinopathy of prematurity.

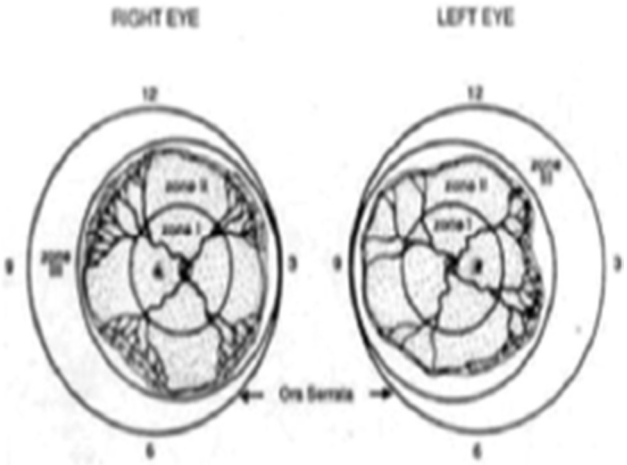

Figure 7: Threshold disease [five contiguous (left eye) or eight cumulative (right eye) total clock hours of stage 3+ in zone I or II] [31].

Most infants at risk will not develop significant ROP; however, proper diagnosis and follow-up is primordial, as short delays in management will result in unequivocal blindness. All efforts are directed to diagnose type 1 ROP and also to identify signs of regression to prevent unnecessary treatment. Regression is defined as the downgrading of ROP stages and/or growth of retinal vessels into a more peripheral zone. Regression commonly occurs safely in most treated and untreated eyes [32]. Active ROP usually begins to regress at a mean age of 38.6 weeks postmenstrual age (PMA). Overall, 90% of the eyes show signs of regression before 44 weeks PMA [33]. Most ROP regresses spontaneously either totally or by passing from a vasoproliferative phase to a fibrotic phase [29].

Signs of regression occur at the junction of the vascular and avascular retina. On serial examinations, the following could be observed:

(1) Change of location of retinopathy towards the periphery
(2) Change of ridge color from salmon pink to white.

(3) Partial resolution is progressing towards complete resolution.
(4) Transgression of vessels through the demarcation line.
(5) Start of the process of replacement of active ROP lesions by scar tissue.

It is also important to follow-up the infant for life owing to many associated ocular comorbidity and cognitive complications.

Screening of retinopathy of prematurity

The screening aims to identify all premature babies whose retinopathy requires treatment. ROP screening must be safe, cost-effective, and target those most at risk [34].

Screening criteria and guidelines

All at-risk infants should be recognized and examined at the proper time. In the United States and Canada, screening criteria are based mainly on the BW, whereas in the European countries, GA is considered more important (Table 2) [35].

In 2013, AAP Section on Ophthalmology, AAO, and AAPOS together with American Association of Certified Orthoptists had revised a previous statement on ROP screening in preterm infants that was published in 2006. They recommend examination of all preterm with BW less than 1500 g or GA of less than 30 weeks in addition to those with BW ranging from 1500 to 2000 g or GA of more than 30 weeks with an unstable clinical course, which makes them at high risk for ROP (as defined by their neonatologist, Table 3).

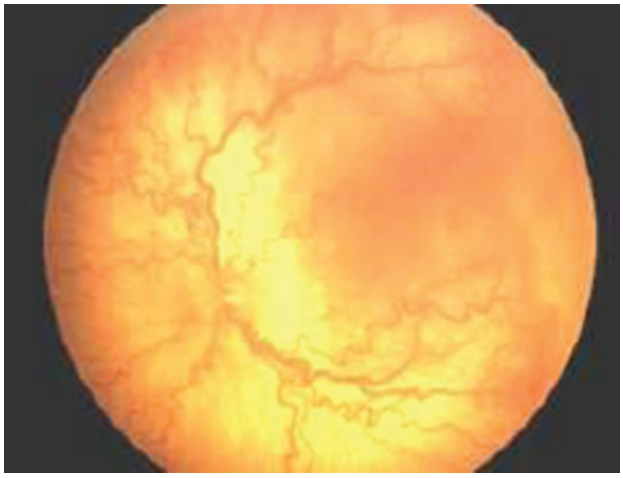

Figure 8: Aggressive posterior retinopathy of prematurity [29].

Subsequent screening examinations

The AAP/AAO/AAPOS Joint Statement in 2013 recommended subsequent examinations according to the schedule in Table 4.

Treatment may be initiated for the following retinal findings:
(1) Zone I: stage 1 or 2 with plus disease
(2) Stage 3 with or without plus disease
(3) Zone II: stage 2 or 3 with plus disease.

Termination of screening examinations

In babies with ROP, screening examinations are stopped when any of these signs are identified according to American Academy of Pediatrics recommendation in 2013.
(1) Zone III retinal vascularization attained without previous zone I or II ROP
(2) Full retinal vascularization near the ora serrata for 360° (this criterion should be used for all ROP treated cases with intravitreal injections only)
(3) PMA of 50 weeks and no prethreshold disease or worse ROP is present
(4) ROP with signs of regression or stabilization seen on at least successive examinations (International Committee for the Classification of Retinopathy of Prematurity, 2005): eyes without ROP changes but with immature incomplete retinal vascularization have to be examined until full retinal vascularization is extending to ora seratta, which usually occurs after 36 weeks PMA [36,37].

Screening examination technique

The eye is dilated with instillation of mydriatic drops about half an hour before the examination. Common combinations include 0.5% tropicamide and 2.5% phenylephrine or 0.5% cyclopentolate and 2.5% phenylephrine (one drop, 5–10 min apart) [34].

All examinations are performed with cardiac and oxygen-saturation monitoring under the supervision of a trained NICU nurse [38].
(1) The common method of examination includes indirect ophthalmoscopy used with a handheld +28 or +30 D. A lid speculum with a gentle indentation for peripheral retinal examination using a Q-tip [30]. Note of the anterior segment status is made, and the extent of vascularization

Table 2: Screening criteria in different countries

Country	Birth weight (g)	Gestational age (weeks)	Additional oxygen	First examination
USA 2006	≤1500	≤32	1500-200 g	4-6 weeks or 31 weeks PMA
England 1996	≤1500	≤31		6-7 weeks
Canada 2000	≤1500	≤30		4-6 weeks
Sweden 1993	≤1500	≤32		5-6 weeks
Denmark	≤1750	≤32		-
The Netherlands 1999	≤1500	<32		4-9 weeks
Germany 2007	≤1500	<32	>3 days	5 weeks

The examination is not recommended earlier than the 4th week of life or before the 30th postmenstrual week [35].

is detected with the observation of the posterior pole vessels for possible plus disease. A retinal drawing is preferably performed, despite being less objective and subject to observer variation [39]

(2) Digital retinal imaging provides photo documentation which is primordial for communicating the disease severity and associated morbidity for teaching NICU staff, for family counseling and follow-up of ROP [40]. Moreover, the image can be transmitted on a network to be analyzed by experts worldwide. Digital cameras are also equipped with fluorescein angiography which confirms subtle neovascularization if needed.

Digital retinal cameras are now commercially available and can be used in the NICUs. Wide-angle cameras are preferred to document the retinal periphery accurately. The RetCam (Clarity Medical Systems Inc., Pleasanton, California, USA) and the PanoCam Pro (Visunex Medical Systems, Fermont, California, USA) are contact wide-angle digital imaging machines. A noncontact ultra-widefield retinal imaging (Optos, Inc. 500 Nickerson Road, Suite 201 Marlborough, MA 01752 USA) is also used but is more cumbersome for neonates.

Some physicians use digital cameras alone or in adjunct to indirect ophthalmoscopy as they believe that imaging or telemedicine cannot replace indirect examination. Both methods of examination are synergistic [39,40].

Treatment of retinopathy of prematurity

Most ROP cases especially stages 1 and 2 regress spontaneously. However, these patients should be monitored at regular intervals until complete resolution as progression may occur. Intervention may be necessary to prevent progression to retinal detachment in advanced cases. Treatment guidelines were suggested in 1988 by the CRYO-ROP study who proposed that threshold ROP was the critical time for treatment [41].

In 2003, ETROP trial revised these indications for treatment. It compared outcomes of early treatment with those performed according to CRYO-ROP study guidelines. There is a significant decrease in unfavorable structural outcomes from 15.6% in eyes treated according to CRYO-ROP guidelines to 9.1% for eyes treated with ETROP [31].

Indications for treatment

According to ETROP, rapid treatment is indicated in prethreshold type 1 ROP, whereas serial examinations without intervention is recommended for prethreshold type 2 ROP [31].

Treatment modalities

Peripheral retinal ablation

Peripheral retinal ablation has proved to be a successful method in treating active ROP. Diode laser ablation with indirect ophthalmoscopy using a confluent or a scatter pattern, leaving from 0.5 to 1.5 burn width between each laser spot to ablate the avascular retina anterior to the fibrovascular ridge reduces the rate of progression of threshold ROP and therefore, reduces retreatment rates [30,42] (Fig. 9).

Laser treatment of the ischemic retina carries many complications [44,45], including high refractive errors, shallow anterior chamber and steep cornea in most patients.

Table 3: Timing of the first screen by gestational age

Gestational age at birth (weeks)	Age at initial examination (weeks)	
	Postmenstrual	Postnatal
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
Older gestational age, high-risk factors		4

American Academy of Pediatrics (2013).

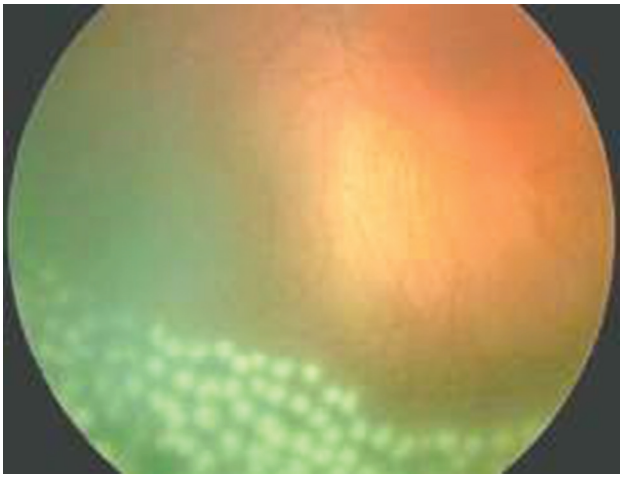

Figure 9: Fundus photo of LASER ablation of the avascular retina [43].

Table 4: Schedule of subsequent examination [36]

	Zone I	Zone II	Zone III
≤ 1 week	Immature vascularization Stage 1 Stage 2 Suspected APROP	Stage 3 Suspected APROP in posterior zone II	
1-2 weeks	Unequivocal regressing ROP	Immature vascularization in posterior zone II-stage 2	
2 weeks		Stage 1 Immature vascularization in anterior zone II Unequivocal regressing ROP	
2-3 weeks			Stage 1 Stage 2

ROP, retinopathy of prematurity.

Cataract may occur, and thermal injury to the long posterior ciliary arteries can produce anterior segment ischemia, glaucoma, corneal haze, corneal and iris burns, posterior synechiae near the pupillary margin, iris atrophy, hyphema and choroidal hemorrhage, which could be associated with laser therapy.

Anti-VEGF agents in ROP may stop or reduce pathologic neovascularization. The rationale for this therapy depends on the high concentration of VEGF in the vitreous suggesting the potential use of intravitreal injections of anti-VEGF for ROP treatment [46].

Many recent reports showed that the anti-VEGF could be a safe and effective treatment for ROP. However, there is concern about the choice of the drug, dose and time of injection as well as local and systemic potential complications [47,48].

The AAP, AAO, AAPOS, and the AACO recommended an intravitreal injection of Bevacizumab (IVB) for those infants with stage 3+ ROP in the zone I, in spite of being not approved by the US FDA for ocular use. Moreover, they strictly advise to use it only after obtaining a detailed informed consent, and long-term follow-up for the potential problems of the drug [36]. Anti-VEGF represents a major step in facilitating the recovery and preventing blinding and devastating complications of ROP without having expensive specialized equipment. Table 5 represents drugs mostly used and dosing.

Antivascular endothelial growth factor as monotherapy

Bevacizumab (Avastin)

The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study compared IVB monotherapy (0.625 mg in 0.025 ml of solution) versus conventional LASER therapy for infants with stage 3 ROP with plus disease in zone 1 or posterior zone 2.

Bevacizumab was found to be significantly superior to laser in zone 1 stage 3+ but not in zone 2. The recurrence rate in infants after Bevacizumab injection was significantly lower (4%) when compared with recurrence rate following the laser (22%). Moreover, peripheral retinal vascularization continued as normal in the Bevacizumab group but not in laser group, which led to the permanent destruction of the peripheral retina. However, the BEAT-ROP study did not clarify safety, long-term outcomes, and proper dosage of the drug [52].

In 2014, Nicoara *et al.* [50] reported using IVB to treat APROP and zone I stage 3+ ROP. After single intravitreal Bevacizumab injection, ROP regression rate was 85.13%. They proved regression of 100% of patients having zone I stage 3+ ROP and 78.84% of patients with AP-ROP without ocular or systemic complications.

Ranibizumab (Lucentis)

Castellanos *et al.* [53] in 2013 published results of three years of follow-up in a small series of ROP cases that had IVR injections (0.25 mg/0.025 ml), which resulted in apparently preserved ocular outcome on long-term follow-up.

Although the shorter half-life of ranibizumab makes it an attractive option, reactivation of ROP is possible [54]. Long-term follow-up after injection until the retina is fully vascularized is primordial in detecting recurrences [51].

It is clear from the literature that the role of anti-VEGF is being established. Regarding the long-term ocular outcomes, there is a definite benefit in reducing the incidence of high myopic changes compared with laser therapy [55].

Surgical management

A significant number of ROP cases progress to retinal detachment (stage 4 and 5 ROP). Once detachment occurs, partially or totally, vitreoretinal surgery is required for visual rehabilitation [56].

Pars plicata vitrectomy is the gold standard of management and is indicated in stage 4B and most stage 5 ROP with severe vitreous traction and when the posterior pole is involved. Late referrals, inadequate laser, poor follow-up, and progression of ROP despite laser or anti-VEGF further complicate this situation. Although surgery achieves ambulatory vision, early intervention, viable retina and optic nerve, and previous laser elsewhere offer better structural and functional outcome.

Early intervention with vitreous surgery for stage 4A ROP achieves better anatomical and visual results [57]. Surgical options include closed vitrectomy with or without lensectomy [56]. Closed vitrectomy permits control of intraocular pressure and allows less manipulation of the globe.

Table 5: Antivascular endothelial growth factor mostly used in the treatment of type 1 retinopathy of prematurity

	Bevcizumab (Avastin)	Ranibuzimab Lucentis
Action	A full anti-VEGF human monoclonal antibody that blocks all VEGF-A isoforms	Antibody fragment (Fab) of humanized anti-VEGF monoclonal antibody that binds and inhibits all biologically active VEGF isoforms
Dose	0.625 mg/0.025 ml	0.25 mg/0.025 ml
Molecule size [49]	149 kD	40 kD
Half-life (days) [49]	8.82	2.88
Regression in zone 1, stage 3+	85.13% [50]	Less regression due to shorter half life [51]
Complications	Myopia++	Myopia+
	Disease relapse+	Disease relapse++

VEGF, vascular endothelial growth factor.

It should be performed after resolution of vascular activity of plus disease. The surgeon may consider vitrectomy with lensectomy in case of the extensive membrane localized close to the lens [57]. Surgery requires a highly skilled pediatric retina surgeon familiar with the anatomy of the infant eye and vigilant enough to address the tractional membranes without inducing retinal tears. The recent introduction of semifluorinated heavy silicone oil (densiron Xtra) is promising in improving results of surgery (Author communication, In Press).

At present, a modern vitreoretinal technique of three-port 23-G or 25-G transconjunctival sutureless lens-sparing vitrectomy is considered an effective technique. It provides smaller surgical wounds and shorter operative time [58].

Lens-sparing vitrectomy is the preferred approach for stage 4A and many stage 4B. It may improve visual rehabilitation after surgery by reducing the risks of aphakic deprivation or anisometropic amblyopia.

Long-term complications can follow vitrectomy surgery (more with stage 5), even when successful, such as recurrence of retinal detachment, strabismus, glaucoma, amblyopia, and retinal degeneration. Long-term follow-up is essential [57].

In conclusion, ROP today needs recognition, understanding, and awareness among ophthalmologists, pediatricians, neonatologists, neonatal and ophthalmic nurses, and obstetricians to tackle this giant burden in the developing world. Egypt has taken major steps in improving neonatal survival rates, and premature children care. The awareness has to extend to a proper ocular examination of children with high risk of developing ROP. The technology of pediatric wide-angle fundus imaging should be adopted in major centers in each governorate. A clear referral system for screening and treatment should be adopted as the only way to prevent blindness from ROP as a major cause of childhood blindness.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet 1997; 350:12–14.
2. UNICEF Children in Egypt 2015, a statistical digest. UNICEF; PP1-5; 2015.
3. El-zanaty F, Way A. Egypt demographic and health survey 2008. Calverton, Maryland (USA): Ministry of health and population. Egypt: National Population Council and ORC Macro; 2009. p. 136.
4. El-Zanaty F, Way A. Egypt Demographic and Health Survey. Ministry of Health and Population, Arab Republic of Egypt; 2008.
5. Kamholz KL, Cole CH, Gray JE, Zupancic JA. Cost-effectiveness of early treatment for retinopathy of prematurity. Pediatrics. 2009;123:262-9.
6. Paysse EA. Retinopathy of prematurity. Available at: *http://www.uptodate.com* [Accessed 8 October 2008].
7. Flynn JT. Retinopathy of prematurity. Pediatr Clin North Am 1987; 34:1487–1515.
8. Hughes S, Yang H, Chan-Ling T. Vascularisation of the human fetal retina: roles of vasculogenesis and angiogenesis. Invest Ophthalmol Vis Sci 2000; 41:1217–1228.
9. Flynn JT, Chan-Ling T. Retinopathy of prematurity: two distinct mechanisms that underlie zone 1 and zone 2 disease. Am J Ophthalmol 2006; 142:46–59.
10. Smith LE. Through the eyes of a child: understanding retinopathy through ROP. Investig Ophthalmol Visual Sci 2008; 49:5177–5182.
11. Ober RR, Palmer EA, Drack AV, Wright KW. Retinopathy of prematurity. Springer, New York. In *Pediatric ophthalmology and strabismus* 2003;pp. 600-628.
12. Penn JS, Madan A, Caldwell RB, Bartoli M, Caldwell RW, Hartnett ME. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 2008; 27:331–371.
13. Othman IS, Khafagy A, El-Mekawey HE, Sabry M. Effect of initial intravitreal bevacizumab (avastin) prior to retinal laser ablation in threshold retinopathy of prematurity. Med J Cairo Univ 2010; 78:347–350.
14. Hameed ERA, Othman I, Sabry R, Sidhom G, Mahmoud R, Gabre A. Vascular Endothelial Growth Factor and Insulin Like Growth Factor-1 Levels in Prematures Serum, its Relation to the Development of Retinopathy of Prematurity. Pediatr Res 2011;70:141. [Internet]. Available from: http://dx.doi.org/10.1038/pr.2011.366. [Last accessed on 2018 Jan].
15. Bassiouny RM, Ellakkany RS, Aboelkhair SA, Mohsen TA, Othman IS. Incidence and risk factors of retinopathy of prematurity in neonatal intensive care units: Mansoura, Egypt. Journal of the Egyptian Ophthalmological Society 2017;110:71.
16. Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P, Zin A, International NO-ROP Group. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. Pediatrics 2005; 115:518–525.
17. Lermann VL, Fortes Filho JB, Procianoy RS. The prevalence of retinopathy of prematurity in very low birth weight newborn infants. J Pediatr (Rio J) 2006; 82:27–32.
18. Sami D, Thompson L, Ramanathan R, Farzavandi S, Wright K. A physiologic low oxygen protocol significantly reduces the incidence of threshold ROP in low-birth-weight premature infants. JAAPOS 2006; 10:67.
19. Choi JY, Han YI, Kim JH, Kim ES, Jeon J. The Most Important Factors for Retinopathy of Prematurity in Preterm Infants. Korean J Perinatol 2014; 25:153–158.
20. STOP-ROP Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity. A randomized, controlled trial I, primary outcomes. Pediatrics 2000; 105:295–310.
21. García-Serrano JL, Ramírez-García MC, Piñar-Molina R. Retinopathy of prematurity in multiple births: risk analysis for plus disease. Arch Soc Esp Oftalmol 2009; 84:191–198.
22. Dani C, Reali MF, Bertini G, Martelli E, Pezzati M. The role of blood transfusions and iron intake on retinopathy of prematurity. Early Hum Dev 2001; 62:57–63.
23. Suk K, Dunbar JA, Liu A, Daher NS, Leng CK, Leng JK, *et al*. Human recombinant erythropoietin and the incidence of retinopathy of prematurity: a multiple regression modes. J AAPOS 2008; 12:233–238.
24. Seiberth V, Linderkamp O. Risk Factors in retinopathy of prematurity a multivariate statistical analysis. Ophthalmologica 2000; 214:131–135.
25. Ali NAM, George J, Joshi N, Chong E. Prevalence of retinopathy of prematurity in Brunei Darussalam. Int J Ophthalmol 2013; 6:381–384.
26. Bassiouny MR. Risk factors associated with retinopathy of prematurity: a study from Oman. J Trop Pediatr 1996; 42:355–358.
27. 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; 55:331.
28. Tsui I, Ebani E, Rosenberg JB, Lin J, Angert RM, Mian U. Patent ductus arteriosus and indomethacin treatment as independent risk factors for plus disease in retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 2013; 50:88–92.
29. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of

prematurity revisited. Arch Ophthalmol 2005; 123:991–999.
30. Palmer EA, Phelps DL, Spencer R, Lutty GA. Retinopathy of Prematurity. In Volume 2: Medical Retina. Elsevier Inc. 2005;Vol. 2-3 p. 1447-1474.
31. 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; 121:1684–1696.
32. Coats DK, Miller AM, Hussein MA, Brady Mccreery KM, Holz E, Paysse EA. Involution of retinopathy of prematurity after laser treatment: factors associated with the development of retinal detachment. Am J Ophthalmol 2005; 140:214–222.
33. Repka MX, Palmer EA. Involution of retinopathy of prematurity. Arch Ophthalmol 2000; 118:645–649.
34. O'Keefe M, Kirwan C. Screening for retinopathy of prematurity. Early Hum Dev 2008; 84:89–94.
35. Jandeck C, Foerster MH. Retinopathy of prematurity: clinical course and treatment. In: Joussen AM, Gardener TW, Kirchhof B, Rayan SJ, editors. *Retinal vascular disease.* Berlin: Springer-Verlag; 2007. 403–417.
36. American Academy of Pediatrics Section on Ophthalmology. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2012:peds-2012.
37. Saunders RA, Hardy RJ, Phelps DL, *et al*.; CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol 2002; 120:1470–1476.
38. Yen KG, Hess D, Burke B, Johnson RA, Feuer WJ, Flynn JT. Telephotoscreening to detect retinopathy of prematurity: a preliminary study of the optimum time to employ digital fundus camera imaging to detect ROP. J AAPOS 2002; 6:64–70.
39. Trese MT. What is the real gold standard for ROP screening? Retina 2008; 28:1–2.
40. Paul Chan RV, Chiang MF, Reynolds JD. Incorporating imaging in a ROP screening practice. J Pediat Ophthalmol Strabismus 2012; 49:134–136.
41. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Arch Ophthalmol 1988; 106:471–479.
42. Rezai KA, Eliott D, Ferrone PJ, Kim RW. Near confluent laser photocoagulation for the treatment of threshold retinopathy of prematurity. Arch Ophthalmol 2005; 123:621–626.
43. Quiram PA, Capone A. Current understanding, and management of retinopathy of prematurity. Curr Opin Ophthalmol 2007; 18:228–234
44. McLoone EM, O'Keefe M, McLoone SF, Lanigana BM. Long-term refractive and biometric outcomes following diode laser therapy for retinopathy of prematurity. J AAPOS 2006; 10:454–459.
45. Nguyen PH, Catt C, Nguyen TX, Pham VT. Refractive outcome of prethreshold retinopathy of prematurity treated by diode laser: follow-up at 5 years. Clin Ophthalmol 2015; 9:1753–1758.
46. Mintz-Hittner HA. Treatment of retinopathy of prematurity with vascular endothelial growth factor inhibitors. Early Hum Dev 2012; 88:937–941.
47. Wallace DK, Wu KY. Current and future trends in the treatment of severe retinopathy of prematurity. Clin Perinatol 2013; 40:297–310.
48. Malik MA, Shukla S, Azad SV, Kaur J. Vascular endothelial growth factor (VEGF-634G/C) polymorphism and retinopathy of prematurity: a meta-analysis. Saudi J Ophthalmol 2014; 28:299–303.
49. Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahshi-Shima C, Kusaka S. Serum concentrations of bevacizumab (Avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol 2012; 153:327–333.
50. Nicoara SD, Nascutzy C, Cristian C, Irimescu I, Stefanut AC, Zaharie G, Drugan T. Outcomes and prognostic factors of intravitreal bevacizumab monotherapy in zone i stage 3+and aggressive posterior retinopathy of prematurity. J Ophthalmol 2015; 2015:1–8.
51. Zhang R, Orge FH. Recurrence of neovascularization status post intravitreal bevacizumab in a patient with retinopathy of prematurity: a case report and review. Austin J Clin Ophthalmol 2015; 2:1041.
52. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+retinopathy of prematurity. N Engl J Med 2011; 364:603–615.
53. Castellanos MAM, Schwartz S, García-Aguirre G, Quiroz-Mercado H. Short-term outcome after intravitreal ranibizumab injections for the treatment of retinopathy of prematurity. Br J Ophthalmol 2013; 97:816–819.
54. Wong RK, Hubschman S, Tsui I. Reactivation of retinopathy of prematurity after ranibizumab treatment. Retina 2015; 35:675–680.
55. Mintz-Hittner HA, Geloneck MM. Review of effects of anti-VEGF treatment on refractive error. Eye Brain 2016; 8:135–140.
56. Capone A, Hartnett ME, Trese MT. Treatment of retinopathy of prematurity: peripheral retinal ablation and vitreoretinal surgery. In: Hartnett ME, editor-In-Chief. *Pediatric retina*. Lippincott Williams and Wilkins; 2005. 392.
57. Rubaltelli DM, Hirose T. Retinopathy of prematurity update. Int Ophthalmol Clin 2008; 48:225–235.
58. Chan-Kai BT, Lauer AK. Transconjunctival sutureless 25-gauge lens-sparing vitrectomy for stage 4 retinopathy of prematurity-related retinal detachments. Retina 2009; 29:854–859.