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

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

Follow this and additional works at: https://jmisr.researchcommons.org/home

Part of the Medical Sciences Commons, and the Medical Specialties Commons

**Recommended Citation**


DOI: https://doi.org/10.4103/JMISR.JMISR_37_18

This Review is brought to you for free and open access by Journal of Medicine in Scientific Research. It has been accepted for inclusion in Journal of Medicine in Scientific Research by an authorized editor of Journal of Medicine in Scientific Research. For more information, please contact m_a_b200481@hotmail.com.
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...
Othman: Retinopathy of prematurity

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-oblitration 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 (PaO2) 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 I 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.
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.

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

<table>
<thead>
<tr>
<th>Type 1: ROP 'high risk'</th>
<th>Type 2: ROP 'low risk'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone I: stage 1 or 2 with plus disease.</td>
<td>Zone I: stage 1 or 2 without plus disease.</td>
</tr>
<tr>
<td>Stage 3 with or without disease.</td>
<td>Zone II: stage 3 without plus disease.</td>
</tr>
<tr>
<td>Zone II: stage 2 or 3 with plus disease.</td>
<td></td>
</tr>
<tr>
<td>ROP, retinopathy of prematurity.</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4:** (a-d) and e show stage 1 (demarcation line), 2 (demarcation ridge), 3 (extra retinal fibrovascular proliferation), 4a (partial retinal detachment excluding the fovea), and 4b (partial retinal detachment including the fovea) ROP, respectively [29]. 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 6:** Plus disease [29].

**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].
(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 premature 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).

**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 serrata, 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

![Figure 8: Aggressive posterior retinopathy of prematurity](image)

<table>
<thead>
<tr>
<th>Table 2: Screening criteria in different countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>USA 2006</td>
</tr>
<tr>
<td>England 1996</td>
</tr>
<tr>
<td>Canada 2000</td>
</tr>
<tr>
<td>Sweden 1993</td>
</tr>
<tr>
<td>Denmark</td>
</tr>
<tr>
<td>The Netherlands 1999</td>
</tr>
<tr>
<td>Germany 2007</td>
</tr>
</tbody>
</table>

*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**

<table>
<thead>
<tr>
<th>Gestational age at birth (weeks)</th>
<th>Age at initial examination (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postmenstrual</td>
</tr>
<tr>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Older gestational age, high-risk factors</td>
<td>4</td>
</tr>
</tbody>
</table>


**Table 4: Schedule of subsequent examination [36]**

<table>
<thead>
<tr>
<th>Zone I</th>
<th>Zone II</th>
<th>Zone III</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 week</td>
<td>Immature vascularization Stage 1</td>
<td>Stage 3 Suspected APROP in posterior zone II</td>
</tr>
<tr>
<td>1-2 weeks</td>
<td>Stage 2</td>
<td>Immature vascularization in posterior zone II-stage 2</td>
</tr>
<tr>
<td>2 weeks</td>
<td>Suspected APROP</td>
<td>Stage 1</td>
</tr>
<tr>
<td>2-3 weeks</td>
<td>Unequivocal regressing ROP</td>
<td>Stage 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immature vascularization in anterior zone II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unequivocal regressing ROP</td>
</tr>
</tbody>
</table>

ROP, retinopathy of prematurity.

---

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

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

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
2. UNICEF Children in Egypt 2015, a statistical digest. UNICEF; PP1-5; 2015.
29. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity.