Retinopathy of Prematurity (ROP) is a vasoproliferative disorder of the developing retina of low birth weight preterm infants. It can lead to blindness in a small but significant percentage of these infants. Because of modern life-support systems capable of keeping tiny premature infants alive, the incidence of retinopathy of prematurity is increasing. A universal classification to quantify disease and efficient screening protocol is extremely useful.

The International Classification of Retinopathy of Prematurity (ICROP) was published in 2 parts, the first in 1984 and later expanded in 1987. It was a consensus statement of an international group of retinopathy of prematurity experts (23 ophthalmologists from 11 countries). This classification has facilitated the development of large multicenter clinical treatment trials and furthered our understanding of this potentially blinding disorder. An international group of pediatric ophthalmologists and retinal specialists (a group of 15 ophthalmologists from 6 countries) has developed a consensus document (ICROP Revisited) in 2005 based on experiences gained on the basis of various multicenter trials that revises original ICROP.

The original ICROP include (1) the location of retinal involvement by zone, (2) the extent of retinal involvement by clock hour, (3) the stage or severity of retinopathy at the junction of the vascularized and avascular retina, and (4) the presence or absence of dilated and tortuous posterior pole vessels (plus disease).

The aspects that differ in 2005 revision from the original classification include introduction of (1) the concept of a more virulent form of retinopathy observed in the tiniest babies (aggressive, posterior ROP), (2) a description of an intermediate level of plus disease (pre-plus) between normal posterior pole vessels and frank plus disease, and (3) a practical clinical tool for estimating the extent of zone-1.

ICROP Revisited classifies ROP as:

**Location of Disease**

The anteroposterior location of the retinopathy has been divided into 3 concentric zones of retinal involvement. Each zone is centered on the optic disc.

Zone I (the innermost zone) consists of a circle, the radius of which extends from the center of the optic disc to twice the distance from the center of the optic disc to the center of the macula. As a practical approach, the approximate temporal extent of zone I can be determined by using a 25- or 28-diopter (D)–condensing lens. By placing the nasal edge of the optic disc at one edge of the field of view, the limit of zone I is at the temporal field of view.

Zone II extends centrifugally from the edge of zone I to the nasal ora serrata (at the 3-o'clock position in the right eye and the 9-o'clock position in the left eye). Any ROP that is continuous and circumferential must by definition fall into 1 of these 2 posterior zones.

Zone III is the residual crescent of retina anterior to zone II. By convention, zones II and III are considered to be mutually exclusive. Retinopathy of prematurity should be considered to be in zone II until it can be determined with confidence that the nasal-most 2 clock hours are vascularized to the ora serrata.

**Extent of Disease**

The extent of disease is recorded as hours of the clock or as 30° sectors. As the observer looks at each eye, the 3-o'clock position is to the right and nasal in the right eye and temporal in the left eye, and the 9-o'clock position is to the left and temporal in the right eye and nasal in the left eye. The boundaries between sectors lie on the clock hour positions; that is, the 12-o'clock sector extends from 12 o'clock to 1 o'clock.

**Stage 1: Demarcation Line**

It is a thin but definite structure that separates the avascular retina anteriorly from the vascularized retina posteriorly. There is abnormal branching or arcading of vessels leading up to the demarcation line that is relatively flat, white, and lies within the plane of the retina. Vascular changes can be apparent prior to the development of the demarcation line, such as dilatation rather than tapering of the peripheral retinal vessels, but these changes are insufficient for the diagnosis of ROP.

**Stage 2: Ridge**

The ridge is the hallmark of stage 2 ROP. It arises in the region of the demarcation line, has height and width, and extends above the plane of the retina. The ridge may change from white to pink and vessels may leave the plane of the retina posterior to the ridge to enter it. Small isolated tufts of neovascular tissue lying on the surface of the retina, commonly called "popcorn" may be seen posterior to this ridge structure.

**Stage 3: Extraretinal Fibrovascular Proliferation**

In stage 3, extraretinal fibrovascular proliferation or neovascularization extends from the ridge into the vitreous. This extraretinal proliferating tissue is continuous with the posterior aspect of the ridge, causing a ragged appearance as the proliferation becomes more extensive. The severity of a stage 3 lesion can be subdivided into mild, moderate, or severe depending on the extent of extraretinal fibrovascular tissue infiltrating the vitreous.
Stage 4: Partial Retinal Detachment

Stage 4 is divided into extrafoveal (4A) and foveal (4B) partial retinal detachments. Stage 4 retinal detachments are generally concave and most are circumferentially oriented. The extent of retinal detachment depends on the number of clock hours of fibrovascular traction and their degree of contraction. Typically, retinal detachments begin at the point of fibrovascular attachment to the vascularized retina. In progressive cases, the fibrous tissue continues to contract and the tractional retinal detachment increases in height, extending both anteriorly and posteriorly.

Stage 5: Total Retinal Detachment

Retinal detachments are generally tractional and may occasionally be exudative. They are usually funnel shaped. The funnel is divided into anterior and posterior parts. Various configurations of funnel in order of frequency are:

Open both anteriorly and posteriorly: The detachment generally has a concave configuration and extends to the optic disc.

Narrow in both anterior and posterior aspects: The detached retina is located just behind the lens.

Open anteriorly but narrowed posteriorly.

Narrow anteriorly and open posteriorly: Least common.

Plus Disease

It refers to increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels. It may increase in severity to include iris vascular engorgement, poor pupillary dilatation (rigid pupil), and vitreous haze. All these signs together in the original classification were referred to as plus disease. Subsequent multicentered clinical trials have used a “standard” photograph to define the minimum amount of vascular dilatation and tortuosity required to make the diagnosis of plus disease. This definition has been further refined in the later clinical trials in which the diagnosis of plus disease could be made if sufficient vascular dilatation and tortuosity are present in at least 2 quadrants of the eye. A + symbol is added to the ROP stage number to designate the presence of plus disease. For example, stage 2 ROP combined with posterior vascular dilatation and tortuosity would be written “stage 2+ ROP.”

Pre-Plus Disease

Pre-plus disease is defined as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal. Over time, the vessel abnormalities of pre-plus may progress to frank plus disease as the vessels dilate and become more tortuous. The presence of pre-plus disease can be noted beside the stage, for example, stage 2 with pre-plus disease.

Aggressive Posterior ROP (AP-ROP)

An uncommon, rapidly progressing, severe form of ROP is designated AP-ROP (Previously referred as “Type II ROP” and “Rush disease” but was not included in ICROP). If untreated, it rapidly progresses to stage 5 ROP without passing through intermediate stages. The characteristic features are its posterior location (most commonly in zone I), prominence of plus disease (dilatation and tortuosity in all 4 quadrants), and ill-defined nature of retinopathy. Because of shunting of vessels in vascularized retina and resultant tortuosity of vessels, it is difficult to distinguish between arterioles and venules. Hemorrhages at the junction of vascularized and avascular retina may be present. It may appear as a flat network of brush like neovascularization at the deceptively featureless junction between vascular and avascular retina. AP-ROP typically extends circumferentially and is often accompanied by a circumferential vessel.

Regression of ROP

In most of the cases, ROP regresses spontaneously by a process of involution or evolution from a vasoproliferative phase to a fibrotic phase. One of the first signs of stabilization of the acute phase of
ROP is failure of the retinopathy to progress to the next stage.\textsuperscript{15} The process of regression occurs largely at the junction of vascular and avascular retina as retinal vascularization advances peripherally. On serial examinations, the anteroposterior location of retinopathy may change from zone I to zone II or from zone II to zone III. The ridge may change in color from salmon pink to white. Involutional sequelae include a broad spectrum of peripheral and posterior retinal and vascular changes that are listed in the Table 1.

The more severe the acute phase of the retinopathy, the more likely involutional changes will be severe as the disease enters the “cicatricial” phase.\textsuperscript{16} During the process of involution, conspicuous features are vascular abnormalities such as prominent areas of retinal avascularity, abnormal branching of vessels with formation of arcades, and telangiectatic vessels. Pigmentary changes may be subtle but more often become large areas of decreased or even increased pigmentation located along blood vessels and in underlying retinal pigment epithelium, as seen through an avascular retina. Circumferential retinovitreous interface changes may be seen as delicate lines or more prominent ridges. In general, the more severe the peripheral changes, the more severe the posterior pole changes. These are tractional phenomena that can vary from minor distortions of foveal architecture to severe displacements of major retinal vessels, usually temporally and often accompanied by dragging of the retina over the optic disc (macular heterotopia or ectopia). Finally, traction and rhegmatogenous retinal detachment and, rarely, exudative detachment can develop as late complications of regressed ROP.

A good screening protocol should be carefully tailored to the population at risk and be modified in accordance with new data as it becomes available. On the basis of experience collected by the international retinopathy of Prematurity classification committee 1982-84, recommendation was to examine eyes after one month, followed by weekly or biweekly examination until there was no risk of developing ROP (evident at the chronological age of 10-12 weeks). Obvious ROP changes required follow up examination for a longer period.

As per the latest guidelines given by American Academy of Pediatrics\textsuperscript{17} in 2006 following protocol is suggested for screening of infants for ROP:

- The following infants should have retinal screening examinations performed after pupillary dilation using binocular indirect ophthalmoscopy to detect ROP:
  - Infants with a birth weight of less than 1500 g or gestational age of 32 weeks or less.
  - Selected infants with a birth weight between 1500 and 2000 g or gestational age of more than 32 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk.

One examination is sufficient only if it unequivocally shows the retina to be fully vascularized in each eye.

Effort should be made to minimize the discomfort and systemic effect of this examination by pretreatment of the eyes with a topical anesthetic agent such as proparacaine; consideration also may be given to the use of pacifiers, oral sucrose, etc.

<table>
<thead>
<tr>
<th>Table 1: Involution Sequelae of Retinopathy of Prematurity</th>
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<tbody>
<tr>
<td><strong>Peripheral changes</strong></td>
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<tr>
<td>Vascular</td>
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<tr>
<td>1. Failure of peripheral retinal vascularization</td>
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<tr>
<td>2. Abnormal nondichotomous branching of retinal vessels</td>
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<td>3. Vascular arcades with circumferential interconnection</td>
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<td>4. Telangiectatic vessels</td>
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<tr>
<td>Retinal</td>
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<tr>
<td>1. Pigmentary changes</td>
</tr>
<tr>
<td>2. Vitreoretinal interface changes</td>
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<tr>
<td>3. Thin retina</td>
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<tr>
<td>4. Peripheral folds</td>
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<tr>
<td>5. Vitreous membranes with or without attachment to the retina</td>
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<tr>
<td>6. Lattice like degeneration</td>
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<tr>
<td>7. Retinal breaks</td>
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<tr>
<td>8. Traction-rhegmatogenous retinal detachment</td>
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<tr>
<td><strong>Posterior changes</strong></td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>1. Vascular tortuosity</td>
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<tr>
<td>2. Straightening of blood vessels in temporal arcades</td>
</tr>
<tr>
<td>3. Decrease in angle of insertion of major temporal arcade</td>
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<tr>
<td>Retinal</td>
</tr>
<tr>
<td>1. Pigmentary changes</td>
</tr>
<tr>
<td>2. Distortion and ectopia of macula</td>
</tr>
<tr>
<td>3. Stretching and folding of retina in macular region leading to periphery</td>
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<tr>
<td>4. Vitreoretinal interface changes</td>
</tr>
<tr>
<td>5. Vitreous membrane</td>
</tr>
<tr>
<td>6. Dragging of retina over optic disc</td>
</tr>
<tr>
<td>7. Traction-rhegmatogenous retinal detachment</td>
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One examination is sufficient only if it unequivocally shows the retina to be fully vascularized in each eye.

Effort should be made to minimize the discomfort and systemic effect of this examination by pretreatment of the eyes with a topical anesthetic agent such as proparacaine; consideration also may be
For detecting ROP potentially damaging to the retina with 99% confidence (Table 2).

- For follow-up examinations following schedule is suggested
  
  **1-week or less follow-up**
  - stage 1 or 2 ROP: zone I
  - stage 3 ROP: zone II
  
  **1- to 2-week follow-up**
  - immature vascularization: zone I—no ROP
  - stage 2 ROP: zone II
  - regressing ROP: zone I
  
  **2-week follow-up**
  - stage 1 ROP: zone II
  - regressing ROP: zone II
  
  **2- to 3-week follow-up**
  - immature vascularization: zone II—no ROP
  - stage 1 or 2 ROP: zone III
  - regressing ROP: zone III

The presence of plus disease in zones I or II suggests that peripheral ablation, rather than observation, is appropriate.20

- Treatment may be initiated for the following retinal findings as per the Early Treatment for Retinopathy of Prematurity Randomized Trial study21:
  - zone I ROP: any stage with plus disease
  - zone I ROP: stage 3—no plus disease
  - zone II: stage 2 or 3 with plus disease

The number of clock hours of disease may no longer be the determining factor in recommending ablative treatment. Treatment should generally be accomplished, when possible, within 72 hours of determination of treatable disease to minimize the risk of retinal detachment.

- The conclusion of acute retinal screening examinations should be based on age and retinal ophthalmoscopic findings.20 The following findings suggest that examinations can be stopped:
  - zone III retinal vascularization attained without previous zone I or II ROP (if there is examiner doubt about the zone or if the postmenstrual age is less than 35 weeks, confirmatory examinations may be warranted);
  - full retinal vascularization;
  - postmenstrual age of 45 weeks and no prethreshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present; or
  - Regression of ROP15 (care must be taken to be sure that there is no abnormal vascular tissue present that is capable of reactivation and progression).

- Parents should be aware of ROP examinations and should be informed if their child has ROP, with subsequent updates on ROP progression. The possible consequences of serious ROP should be discussed when there is a significant risk of poor visual outcome.

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### Table 2: Timing of first examination based on gestational age at birth

<table>
<thead>
<tr>
<th>Gestational age in weeks</th>
<th>Age at initial examination in weeks</th>
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<tbody>
<tr>
<td></td>
<td>Postmenstrual age</td>
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<tr>
<td>22*</td>
<td>31*</td>
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<tr>
<td>23*</td>
<td>31*</td>
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<td>24</td>
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</table>

*This is tentative rather than evidence-based for infants with a gestational age of 22 to 23 weeks because of the small number of survivors in these gestational-age categories.*
• Responsibility for examination and follow-up of infants at risk of ROP must be carefully defined by each NICU. If hospital discharge or transfer to another neonatal unit or hospital is contemplated before retinal maturation into zone III has taken place or if the infant has been treated by ablation for ROP and is not yet fully healed, the availability of appropriate follow-up ophthalmologic examination must be ensured, and specific arrangement for that examination must be made before such discharge or transfer occurs. If responsibility for arranging follow-up ophthalmologic care after discharge is delegated to the parents, they should be made to understand the potential for severe visual loss, including blindness; that there is a critical time window to be met if treatment is to be successful; and that timely follow-up examination is essential to successful treatment.

Pediatricians and other practitioners who care for infants who have had ROP, regardless of whether they require treatment, should be aware that these infants may be at risk of other seemingly unrelated visual disorders such as strabismus, amblyopia, cataract, etc. Ophthalmologic follow-up for these potential problems after discharge from the NICU is necessary.

References


