

# Editorial: retinopathy of prematurity; a synopsis

Volume 4 Issue 1 - 2016

**Abbreviations:** ROP: Retinopathy of Prematurity; ETROP: Retinopathy of Prematurity; VEGF: Vascular Endothelial Growth Factor; UCB: Umbilical Cord Blood

Retinopathy of prematurity (ROP) or retrolental fibroplasia is a vasoproliferative disorder that occurs to the retina of premature infants and was first diagnosed in 1942 by Terry.<sup>1</sup> ROP in severe cases damage the retina by detaching from the wall of the eye and possibly causing visual impairment and blindness.<sup>2,3</sup> In the last 7 decades, there have been several advancements in the understanding and treatment of ROP. In spite of these advances, there are approximately 50,000-60,000 children globally who are blind as a result of ROP.<sup>4</sup> Every year in the U.S. about 14,000 get affected by ROP out of which about 1,100-1,500 develop advanced or severe diseases which require medical treatment and eventually 400-600 infants become blind.<sup>5</sup> In Middle East, over the last 10 years there is an increase observed in the ROP incidence from 23.1% to 56%. The burden of ROP is increasing rapidly and there is a need to focus on the earlier intervention and implementation of effective treatment strategies as this is a lifetime disease.<sup>6</sup>

The major risk factors include prematurity, low birth weight, time of achievement of full feeding and hyperoxia. Other possible risk factors include anemia, blood transfusion, respiratory distress, and breathing difficulties. The underlying physiologic mechanism through which breast milk may protect against the development of ROP may reflect the antioxidant and immune protective properties of human milk.<sup>2,3,7,25</sup>

ROP screening is generally done in babies whose birth weight is <1500 g or  $\leq$ 32 weeks of gestation or selected infants by their neonatologist who are at higher risk. ROP is classified based on the location (zones I-III) and severity (stages I-V) as well as plus and pre-plus disease. Screening is required when ROP is severe i.e., from 3 to 18 weeks after birth depending on gestational age. Screening also depends on the decision of the management, which includes no further examination as the ROP is regressing, further examination is required after an interval of time or treatment is required immediately within 48 hours.<sup>4</sup> Consanguinity may also play a role in ROP development and further genetic studies may help in elucidating the pathogenesis.<sup>8</sup> In addition, Trisomy 21 significantly reduces ROP in very low birth weight infants. This can be developed into a laboratory-based ROP screening tool.<sup>9</sup>

## Treatment

Experience in delivering the optimal care for ROP patients is required. The rate of treatment and re-treatment is inversely proportional to the experience of the ophthalmologist's with managing ROP.<sup>10</sup> The Early Treatment for Retinopathy of Prematurity (ETROP) study produced favorable results yielding new guidelines for treatment of infants with ROP. These included, early treatment of high-risk prethreshold ROP improves retinal and visual outcomes at 9 months corrected age and also indicated that early treatment can be avoided for certain eyes and be observed for signs of disease progression.<sup>11</sup> Katargina L study also showed that modern methods like optical

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**Received:** January 17, 2016 | **Published:** January 21, 2016

coherence tomography and extraretinal growth parameters are an important criteria for the early diagnosis and helps in the detection of a preclinical negative trend in cicatricial ROP.<sup>12</sup>

Treatment strategies for ROP include surgeries (like vitrectomy and scleral buckle), laser or cryotherapy etc. According to the CRYO-ROP trial, timely ablation (laser photocoagulation or retinal photoablation) of the avascular peripheral retina decreases the incidence by 40%. However, the failure rate of the therapy remained high. Hence frequent follow up and timely surgical intervention is warranted.<sup>13</sup> There is a correlation between the neovascular drive in ROP eyes with stage 3 disease and intraocular vascular endothelial growth factor (VEGF) levels that was successfully treated with intravitreal bevacizumab.<sup>14</sup> The BEAT-ROP trial presented the results that eyes with zone I threshold disease was better managed by bevacizumab than with conventional laser and zone II eyes was managed similarly by both the therapies. Most ROPs required single bevacizumab injection.<sup>15-17</sup> The outcomes of ROP treatment with bevacizumab after 2 years showed that 82% of infants have not had recurrence or any other complications that required intraocular surgery. Also early treatment with bevacizumab for cases of neovascularization can prevent bleeding and avoid surgical complication.<sup>18,19</sup> To control the VEGF levels that acts as a key factor in angiogenesis regulation in the developing retina as well as central nervous system, anti-VEGF drugs are used. Nevertheless, concerns remain due to their potential local and systemic adverse effects.<sup>20</sup> A powerful antioxidant and a VEGF inhibitor, D-penicillamine which when used to treat other disease that premature infants have, the treated infants had less ROP occurrence. However, no significant benefits of D-penicillamine was observed for the outcomes of ROP, death or development of nerves and hence not recommended.<sup>21</sup> Stem cell therapy with the help of umbilical cord blood (UCB) could present as an alternative treatment for ROP in preterm infants. To validate this, further in vivo studies are warranted.<sup>22</sup>

## Prevention of ROP<sup>3,16,23-25</sup>

- Regulation of oxygen supply as both hypoxia and hyperoxia is detrimental to the baby so oxygen therapy should be carefully

monitored by pulse oximetry. The saturation limit should be maintained between 90-95%.

- ii. Permissive hypercapnia: reduced carbon dioxide is a risk factor for ROP. But this factor enables lower ventilator settings reducing the occurrence of lung diseases which requires prolonged oxygen use.
- iii. Cautious use of blood transfusions: Adult RBCs are rich in 2,3-diphosphoglycerate and adult haemoglobin which binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue.
- iv. Human milk feeding potentially plays a protective role in preventing any-stage ROP and severe ROP for very low birth weight infants.
- v. Strict clinical and electronic monitoring which helps in early detection of disorders making a prompt treatment.
- vi. Prenatal steroids help in preventing respiratory distress and intraventricular haemorrhage, which are the two important risk factors for ROP.
- vii. Screening program with a proper neonatal unit, effective ROP surveillance and management decreases the severity of disease.

## Conclusion

Risk factor analysis helps in understanding ROP development and can predict it in severe preterm infants. Hospitals should employ well-trained and experienced ophthalmologists for early ROP screening and treatment. Physicians should collaborate with neonatal intensive care unit coordinators for a good tracking system, which includes initial screenings to follow-up until post-discharge care. A high priority is given to the screening program conducted by the World Health Organization's "Vision 2020 program". These help in the institution of appropriate treatment to prevent blindness and offer child a better overall development.

## Acknowledgments

None.

## Conflicts of interest

The authors declare there is no conflict of interests.

## Funding

None.

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