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Review Article

Retinopathy of Prematurity Epidemiology, Diagnosis, and Management

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Abstract

Introduction: Retinopathy of prematurity (ROP) is a disease that threatens the eyesight of preterm and low-birthweight infants. Historically the disease was more common in developed countries, but now its occurrence has increased in developing countries as well. The disease progresses in two phases, namely vaso-occlusion and vaso-proliferation. Various risk factors exist for ROP, according to which criteria for the screening are developed in different countries. Diagnosis is usually made by using an ophthalmoscope and graded according to the amount of vaso-proliferation. Based on grading, treatment may be carried out medically, surgically, and most commonly, by using LASER.

Aim of Work: The aim of this study is to review retinopathy of prematurity.

Materials and Methods: Comprehensive research of retinopathy of prematurity epidemiology, Etiopathogenesis, and management. PUBMED search engines were the primary database used for the search process from the year 1988 to 2022.

Conclusion: Despite decades of research, retinopathy of prematurity continues to be a trial for neonatal ophthalmologists. As maternity healthcare improves across the globe, more cases of ROP are emerging. Several treatment strategies exist that significantly reduce the occurrence of ROP, but they also carry risks of complications. Preventive measures with better maternal healthcare, early detection with modern biomarkers, and timely intervention with appropriate therapy can improve the lives of thousands of voiceless infants.

Keywords: *Retinopathy of Prematurity; Premature Infant; Vasoproliferative Eye Disease; Low Birth Weight*

Introduction

Retinopathy of prematurity (ROP) is a vision-threatening disease where vasoproliferation affects the retina of infants who are born prematurely with low birth weight. Historically ROP has been associated with the administration of a high concentration of oxygenation followed by a phase of hypoxia-mediated vasoproliferation. ROP was primarily seen in developed countries in the past, but now it is increasingly common in developing countries where mother and childcare has improved. In this review, we will discuss the history, epidemiology, etiopathogenesis, clinical features, investigations and management of ROP [1].

History

ROP was initially called retrolental fibroplasia, as described by Terry in 1942, whereas its modern name was created in 1951. In the late 1940s, newly designed incubators for oxygenation of newborns were introduced in Britain. The casual use of these oxygen incubators led Mary Grosse of Birmingham to suspect increased cases of blindness among newborns in 1951. Kate Campbell found a similar association between casual use of oxygen incubators and blindness among babies in Australia. Though it became essential to withdraw oxygenation if ROP was detected, it was equally important to do it gradually as studies showed a rapid increase in ROP if oxygen was suddenly stopped [2].

As supplemental oxygen application was reduced in 1954, there was an increase in the incidence of spastic diplegia and a decrease in ROP. Therefore, long-term neurological follow-up of ROP survivors was instructed. During the 1960s, with an increased effort to save more and more preterm infants, there was a reappearance of ROP cases in even more significant numbers. Similar trends were seen in developing countries where there was an improved effort to save preterm babies. In the 1970s and 1980s, oxygen saturation measuring devices such as transcutaneous O_2 electrodes and pulse oximetry emerged, but we could never come up with an ideal oxygenation amount that would counter both ROP as well as lung and brain diseases [2].

Epidemiology

Up to 10% of babies are born preterm (less than 37 weeks of gestation) globally, and it is the commonest cause of neonatal fatality. Over the years, several studies have found a variable incidence of ROP among preterm and low birth weight babies due to non-uniform study designs. In a retrospective cohort study including 29 hospitals in the United States and Canada, between 2006 and 2011, 7483 preterm infants were examined for ROP. 3224 (43.1%) developed ROP, whereas 12.5% had severe ROP with an almost always birth weight below 1251 grams [3].

A prospective study in Sweden reported a retinopathy incidence of 73% (368/506) with 35% (176/506) of severe cases among babies born preterm (gestation below 27 weeks) [4]. Another study in Norway reported 33% (95/290) of ROP cases with preterm babies (gestation below 28 weeks) [5]. Belgian investigators, on the other hand, reported 26% (45/175) cases of severe ROP with a similar gestational period as the Swedish study [6]. The incidence of ROP among different regions of India ranges from 38 to 47%, where gestation of fewer than 35 weeks is considered preterm [7].

Country	Gestational age (weeks)	Birth weight (grams)
USA	< 31	< 1500
India	< 35	< 2000
Kenya	< 34	< 1750
Mexico	< 34	< 1750
Philippines	< 35	< 2000
Romania	< 32	< 1500
Thailand	< 30	< 1500
Venezuela	< 35	< 1750

Table: *Screening criteria for various nations [7].*

Etiopathogenesis

Retinal blood vessels start to grow from the optic nerve at around 16 weeks of gestation and continue to develop until full term. Infants born preterm end up with an underdeveloped retinal vascular supply and capillaries continue to grow after birth. ROP usually occurs in two phases. The first is the vaso-obliteration phase, where there is suppression of vessel formation due to decreased growth factors and increased oxygenation, which the infant gets exposed to. Next comes the vaso-proliferation phase, where abnormal blood vessels are formed due to hypoxic stress and increased angiogenic factors [8].

The over and under-expression of vascular endothelial growth factor (VEGF) plays a major role in both phases of ROP. When preterm babies are born, they are usually in need of supplemental oxygen because respiratory stress syndrome is common in them. Hyperoxia, caused by supplemental oxygenation, suppresses the VEGF-driven capillary development (Phase 1). Hyperoxia not only suppresses VEGF but also induces vaso-obliteration due to apoptosis of vascular endothelial cells. Intra-uterine oxygen pressure is typically low, where even room air can create a hyperoxic environment post-birth. Vaso-obliteration can be prevented using exogenous VEGF, which helps in the survival of the existing vessels [9].

The vasoproliferative (phase 2) starts at around 32 - 34 weeks of gestational age. The neural retina becomes metabolically active and the loss of blood vessels from phase 1 leads to a hypoxic environment. Oxygen deficient environment leads to over-production of VEGF and proliferation of vessels. The newly formed vessels are usually leaky and fibrous scar tissue formation leads to retinal detachment. The majority of ROP cases are self-limiting, but up to 10% of cases progress to severe forms leading to partial or complete blindness [10].

Insulin-like growth factor 1 (IGF 1) and growth hormone (GH) also play a role in neovascularization in phase 2 of ROP. In studies on transgenic mice, GH/IGF 1 receptor antagonist inhibited neovascularisation in the proliferative phase of ROP. Moreover, the level of VEGF seemed to be unaffected by GH/IGF 1 suppression. The study showed GH/IGF 1 to have played more of a permissive role in maximal VEGF stimulation [11].

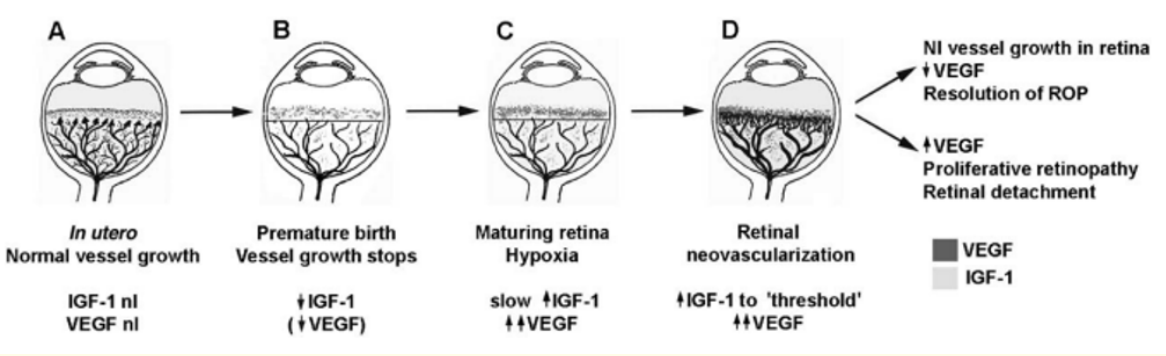

Figure 1: *IGF 1/VEGF mediated control of vascularization in the development of ROP [9].*

Risk factors

Oxygen

The debate regarding the correct amount of oxygen supplementation to avoid both retinopathies of prematurity and infant mortality remains unsettled. Many large-scale studies have attempted to investigate the oxygen saturation (SpO_2) during phase 1 of ROP against

infant morbidity and mortality. In a national survey in the United States, preterm and low birth weight infants (in the 1st two weeks following birth) who were administered either oxygen with either SpO_2 of greater than 98% or less than/equal to 98% were studied. They found the incidence of retinal ablation surgery (severe retinopathy) in 5.5% of cases in the first group vs. 3.0% in the latter group. After two weeks following birth, the incidence of retinal ablation surgery was 3.3% when the maximum SpO_2 was > 92 vs. 1.3% when the max SpO_2 was ≤ 92% [12]. In 2010, a study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT trial) was conducted comparing 1316 infants with lower target SpO_2 range (85 to 89%) to infants with higher target SpO_2 range (91 to 95%). Severe ROP rates in the lower target SpO_2 group were 28% against 32% in the higher target SpO_2 group. The mortality rate was higher in the earlier group when compared to the latter (19.9% vs. 16.2%) [13].

Gestational age and birth weight

Premature birth and low birth weight are both major factors when considering retinopathy of prematurity because both these factors are an indirect measure of how immature the retina of an infant is at birth. Additionally, the more premature a birth is, the more postnatal insults the infant has to bear. Gestational age in weeks and birthweight in grams are measured and the screening criteria for such preterm infants are variable among different locations across the globe [10].

Insulin-like growth factor 1 (IGF 1)

Low postnatal serum IGF 1 has a strong association with the subsequent development of ROP. As discussed earlier, IGF 1 works like a permissive factor for VEGF in the development of retinal vasculature in phase 1 of ROP. Hellstrom., *et al*. conducted a prospective, longitudinal study where they weakly measured serum IGF 1 in 84 preterm infants at birth until relieved from the hospital. They noticed that lower serum IGF 1 concentration was associated with subsequent development of ROP along with other complications of preterm birth [14].

Examination and clinical staging

The primary method of investigation for ROP is the eye examination using an ophthalmoscope. An eye exam is a painful and expensive procedure that should be carried out only if it's beneficial to the patient. Several screening criteria exist across the globe to narrow down the suspected infants and these screening criteria constantly get updated as new data pours in. Screening cut-offs usually constitute 30 - 35 weeks of gestational age and 1500 - 2000 grams of birth weight [10].

Eye examination

ROP eye examinations are usually conducted every 1 to 3 weeks on suspected individuals depending on the disease severity. A certain protocol must be followed for an eye examination as it may be painful and dangerous for the infant [15]:

- Pupils are dilated with mydriatic ophthalmic drops 1 - 2 hours before an eye exam.
- Cardiorespiratory monitors are attached during pupillary dilation.
- Topical anesthetic drops are given just prior to an eye exam.
- A speculum retracts the eyelids during the exam.
- A depressor is used to hold the eyeball in position and an ophthalmoscope is used to examine the retina. Each eye is examined separately.
- The infant is constantly monitored during and after the procedure for heart rate and respiratory distress [15].

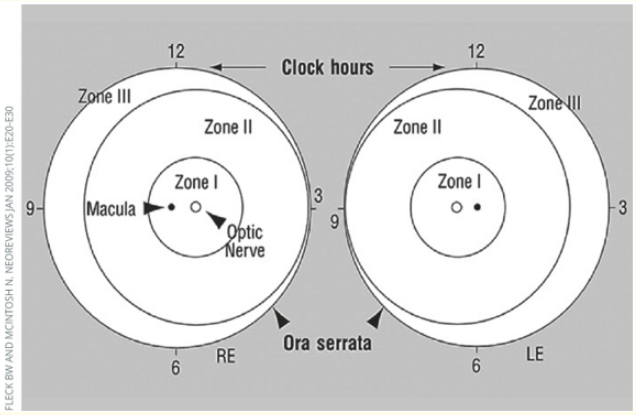

Figure 2: *Orbit examined under various zones: 1, 2 and 3 [16].*

Zones:

- **Zone 1:** Consists of a little circle around the optic disc on the retina.
- **Zone 2:** Consists of a larger circle around zone 1 which touches the ora serrata on the nasal side.
- **Zone 3:** Is a crescent surrounding zone 2 and consists of the remaining part of the retina on the temporal side [16].

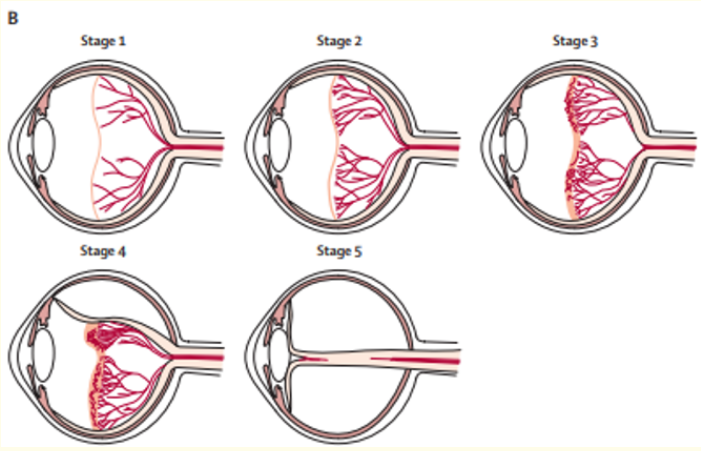

Figure 3: *Stages of retinopathy [16].*

Stages:

- **Stage 1:** A whitish demarcation line exists between vascularized and avascularised parts of the retina.
- **Stage 2:** The demarcation line turns into a ridge in 3 dimensions.

- **Stage 3:** Blood vessels proliferate one ridge seen in stage 2.
- **Stage 4:** There is partial or subtotal retinal detachment.
- **Stage 5**: Retina is completely detached [16].

Clinical images in ophthalmoscope [16]

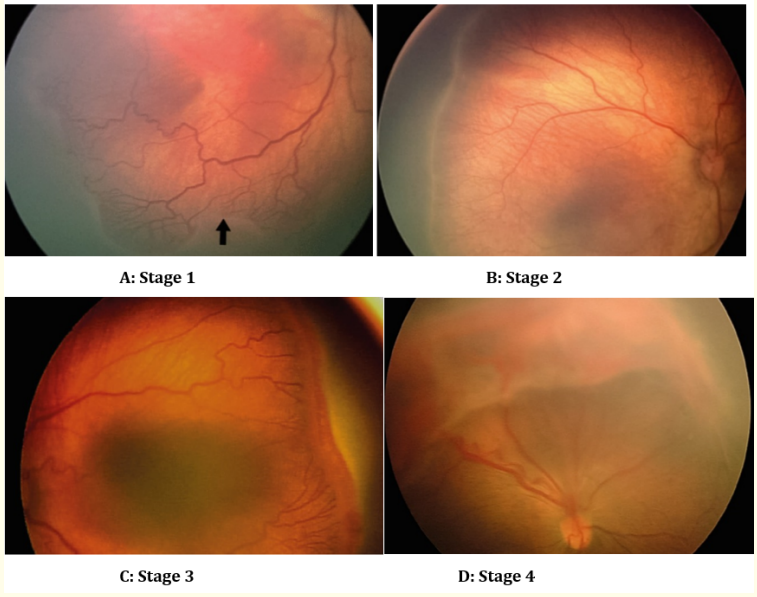

Figure 4

Biomarkers

The diagnosis of ROP is dependent on the expertise of ophthalmologists with a great deal of subjectivity and variability. Infants are voiceless and cannot describe changes occurring in their vision. Therefore, it becomes essential to use various ROP biomarkers that may aid in the diagnosis, treatment planning, and prognosis of this disease. Biomarkers can come in the form of metabolites, cytokines and growth factors, ncRNAs, gut microbiota, iconography, oxidative stress biomarkers, etc. These biomarkers can easily be obtained from the blood, serum, urine and feces of infants [17].

Nilson., *et al*. found that low concentrations of sphingosine-1-phosphate found in infants' serum strongly suggest severe retinopathy of prematurity [18]. Another study indicated that several inflammatory mediators such as IL-6 and IL-8 and angiogenic mediators such as endoglin, endostatin and (IGFBP)-2 found in amniotic fluid are associated with the incidence of ROP [19]. Recently, non-coding RNAs have been studied as possible biomarkers of ROP. Metin., *et al*. studied 13 ROP and 15 non-ROP premature infants. They found elevated levels of 23a and miR-200b-3p and reduced levels of miR-27b-3p and miR-214-3p in premature infants with ROP [20]. Others have also studied changes in the maternal gut microbiota as a potential biomarker for ROP in premature infants. Some studies have suggested that *Enterobacteriaceae* species grow a few weeks before ROP is diagnosed [21].

Treatment

Phase 1

During the vaso-obliteration phase of ROP development, certain strategies may have benefits, such as providing VEGF, IGF 1, placental growth factor and erythropoietin. However, clinical trials are yet to prove their efficacy in the management of ROP [22].

Phase 2

Historically, cryotherapy remained the sole surgical management strategy for the treatment of ROP. Cryotherapy uses a probe to freeze the abnormal growth of blood vessels. In a multicenter clinical trial, transscleral cryotherapy was applied randomly to one eye while keeping the other as a control in 172 infants. After three months, infants were examined for unfavorable outcomes such as posterior retinal detachment, retinal fold involving the macula or retrolental tissue. The unfavorable outcome was 43% in control eyes and only 21.8% in the treated eyes. The study suggested that cryotherapy can reduce up to 50% of the ROP risk [23].

LASER proved to be superior to cryotherapy because it provided better access to avascular parts of the retina where surgical access was required to advance the cryoprobe. LASER is a highly effective treatment modality with regression rates after the procedure to be nearly 93% and 100% for threshold and pre-threshold ROP, respectively. Commonly used LASERS are indirect infrared diode lasers, and four-frequency doubled Nd: YAG lasers which are applied via Laser indirect ophthalmoscope (LIO) as a delivery media. LASER does come with some complications, such as peripheral vision loss, cataracts, myopia and phthisis bulbi. LASER comes with several complications as well, such as peripheral vision loss, cataracts, myopia and phthisis bulbi [24].

VEGF inhibitors can potentially benefit in cases where LASER is not achievable, such as poor pupillary dilatation, corneal opacification, vitreous haze, and hemorrhage. VEGF inhibitors cause lesser structural complications and reach posterior ischemic zones. Bevacizumab, intravitreal ranibizumab (IVR) and intravitreal aflibercept (IVA) are some anti-VEGF agents. Studies with intravitreal bevacizumab (IVB) showed the recurrence rate of ROP to be only 4% when compared to 22% of conventional LASER. In a meta-analysis, the retreatment rate in the anti-VEGF group was significantly higher when compared to the LASER group, whereas the incidence of ocular complications was lower in the anti-VEGF group [25].

Certain surgical interventions also exist in advanced stages of ROP, such as stages 4 and 5. Stage 4 may require scleral buckling and lens-sparing vitrectomy (LSV). Stage 5 may require more aggressive procedures such as lensectomy along with vitrectomy (LV) or open-sky vitrectomy (OSV). Success from surgical management in stage 4 can range between 84 - 100%, whereas, in stage 5, it reaches only 14.3 - 45.5%. Similarly, the recurrence rate in stage 4 is 5% compared to 22% in stage 5 [26].

Conclusion

Despite decades of research, retinopathy of prematurity continues to be a trial for neonatal ophthalmologists. As maternity healthcare improves across the globe, more cases of ROP are emerging. Several treatment strategies exist that significantly reduce the occurrence of ROP, but they also carry risks of complications. Preventive measures with better maternal healthcare, early detection with modern biomarkers and timely intervention with appropriate therapy can improve lives of thousands of voiceless infants.

Bibliography

1. Shah PK., *et al*. "Retinopathy of prematurity: Past, present and future". *World Journal of Clinical Pediatrics* 5.1 (2016): 35.

2. Silverman WA. "A cautionary tale about supplemental oxygen: the albatross of neonatal medicine". *Pediatrics-Springfield* 113.2 (2004): 394-397.

3. Quinn G E., *et al*. "Incidence and early course of retinopathy of prematurity: secondary analysis of the postnatal growth and retinopathy of prematurity (G-ROP) study". *JAMA Ophthalmology* 136.12 (2018): 1383-1389.

4. Austeng D., *et al*. "Incidence of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden". *Archives of Ophthalmology* 127.10 (2009): 1315-1319.

5. Markestad T., *et al*. "Early death, morbidity, and need of treatment among extremely premature infants". *Pediatrics* 115.5 (2005): 1289-1298.

6. Allegaert K., *et al*. "Threshold retinopathy at threshold of viability: the EpiBel study". *British Journal of Ophthalmology* 88.2 (2004): 239-242.

7. Bowe T., *et al*. "The current state of retinopathy of prematurity in India, Kenya, Mexico, Nigeria, Philippines, Romania, Thailand, and Venezuela". *Digital Journal of Ophthalmology: DJO* 25.4 (2019): 49.

8. Jang JH and Kim YC. "Retinal vascular development in an immature retina at 33-34 weeks postmenstrual age predicts retinopathy of prematurity". *Scientific Reports* 10.1 (2020): 1-8.

9. Smith LE. "Pathogenesis of retinopathy of prematurity". *Seminars in Neonatology* 8.6 (2003): 469-473.

10. Hellström A., *et al*. "Retinopathy of prematurity". *The Lancet* 382.9902 (2013): 1445-1457.

11. Smith LE., *et al*. "Regulation of vascular endothelial growth factor-dependent retinal neovascularization by insulin-like growth factor-1 receptor". *Nature Medicine* 5.12 (1999): 1390-1395.

12. Anderson CG., *et al*. "Retinopathy of prematurity and pulse oximetry: a national survey of recent practices". *Journal of Perinatology* 24.3 (2004): 164-168.

13. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. "Target ranges of oxygen saturation in extremely preterm infants". *New England Journal of Medicine* 362.21 (2010): 1959-1969.

14. Hellstrom A., *et al*. "Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth". *Pediatrics* 112.5 (2003): 1016-1020.

15. Mitchell AJ., *et al*. "Physiologic effects of retinopathy of prematurity screening examinations". *Advances in Neonatal Care: Official Journal of the National Association of Neonatal Nurses* 11.4 (2011): 291.

16. Molinari A., *et al*. "Classifying retinopathy of prematurity". *Community Eye Health* 30.99 (2017): 55.

17. Tan W., *et al*. "Novel Potential Biomarkers for Retinopathy of Prematurity". *Frontiers in Medicine* (2022): 143.

18. Nilsson AK., *et al*. "Sphingolipidomics of serum in extremely preterm infants: Association between low sphingosine-1-phosphate levels and severe retinopathy of prematurity". *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids* 1866.7 (2021): 158939.

19. Woo SJ., *et al*. "Inflammatory and angiogenic mediators in amniotic fluid are associated with the development of retinopathy of prematurity in preterm infants". *Investigative Ophthalmology and Visual Science* 61.5 (2020): 42-42.

20. Metin T., *et al*. "Evaluation of the plasma microRNA levels in stage 3 premature retinopathy with plus disease: preliminary study". *Eye* 32.2 (2018): 415-420.

21. Mammas IN and Spandidos DA. "Retinopathy of prematurity and neonatal gut microbiome: An interview with Professor Dimitra Skondra, Associate Professor of Ophthalmology and Vitreoretinal Surgeon at The University of Chicago (USA)". *Experimental and Therapeutic Medicine* 20.6 (2020): 1-1.

22. Hansen ED and Hartnett ME. "A review of treatment for retinopathy of prematurity". *Expert Review of Ophthalmology* 14.2 (2019): 73-87.

23. Cryotherapy for Retinopathy of Prematurity Cooperative Group. "Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results". *Pediatrics* 81.5 (1988): 697-706.

24. Dhawan A., *et al*. "Structural sequelae and refractive outcome after successful laser treatment for threshold retinopathy of prematurity". *Journal of Pediatric Ophthalmology and Strabismus* 45.6 (2008): 356-361.

25. Li Z., *et al*. "Comparison of efficacy between anti-vascular endothelial growth factor (VEGF) and laser treatment in Type-1 and threshold retinopathy of prematurity (ROP)". *BMC Ophthalmology* 18.1 (2018): 1-10.

26. Kondo H., *et al*. "Late recurrence of retinal detachment following successful vitreous surgery for stages 4B and 5 retinopathy of prematurity". *American Journal of Ophthalmology* 147.4 (2009): 661-666.

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