ACTA MEDICA LITUANICA. 2006. VOLUME 13 No. 3. P. 141–146

Multifactorial risk environment for retinopathy of prematurity

Nijolė Drazdienė*

Centre of Neonatology,
Vilnius University,
Antakalnio 57, LT-10200 Vilnius,
Lithuania

Rasa Bagdonienė

Department of Ophthalmology,
Vilnius University Hospital,
Vilnius, Lithuania

Rasa Sirtautienė

Department of Ophthalmology,
Vilnius University Hospital Santariskiu Clinics,
Vilnius, Lithuania

Nijolė Vezbergienė

Centre of Neonatology,
Vilnius University Children's Hospital,
Vilnius, Lithuania

Viktorija Sliesoraitienė

Centre of Rehabilitation,
Vilnius Gediminas Technical University,
Vilnius University Children's Hospital,
Vilnius, Lithuania

Ieva Sliesoraitytė

Kaunas University of Medicine,
Kaunas, Lithuania

Background: Retinopathy of prematurity (ROP) might be prevented by a timely diagnosis and appropriate treatment applied according to the risk factors. The goal of our research was to combine the optimal clinical and epidemiological indicators for ROP risk detection.

Materials and methods: A retrospective observational research was carried out at Clinic of Neonatology of Vilnius University Children's Hospital. The research combined examination of epidemiological and clinical characteristics of premature neonates born in 2005 and analysis of ROP protocols. Multifactorial risk environment for ROP pathological process development was elucidated.

Results: The infants' age at ROP onset was four to six weeks. Their mean gestational age was 28.1 ± 0.9 weeks, the mean birth weight being 1250 ± 214 g. Infants at the greatest risk of ROP weighed 1500 g or less at birth ($p < 0.001$), and their gestational age was 30 weeks or less ($p < 0.05$). An inverse relationship was found between the incidence and severity of ROP and birth weight and gestational age ($r_1 = -0.8$; $r_2 = -0.7$; $p < 0.01$). Low Apgar scale rates were positively associated with ROP stage and accordingly with a high ROP risk level ($r_3 = 0.9$; $p < 0.001$). Delivery and pregnancy failure increase the ROP pattern as following infections and bleeding during delivery are the leading pathological status elevating ROP stage. Oxygen therapy had been applied in all ROP stages. Concomitant neonate pathologies range within a moderate to high risk level for ROP development ($p < 0.001$).

Conclusions: The tool based on artificial neural networks has the potentiality of identifying the risk level for ROP development with high sensitivity considering positive and negative predictive values.

Key words: retinopathy of prematurity, risk factors, artificial neural networks

* Corresponding author. E-mail: nijole.drazdiene@vmul.vu.lt

BACKGROUND

Recent advances in perinatal and neonatal care, including the use of surfactant therapy and new methods of mechanical ventilation have contributed to the survival of premature infants of extremely low birth weight and as premature as 22 to 25 weeks of gestational age (1). The more than a decade continuing progress and the successful perinatology programs have improved most neonatal outcomes, however, resulting in the increased risk of developing retinopathy of prematurity (ROP) and the subsequent visual disability and blindness from ROP (1, 2). ROP is a leading cause of childhood blindness (3, 4), moreover, it is recognized with increasing frequency in developing regions all over the world, accounting for up to 10% of childhood blindness (5–7). Currently, ROP is an important cause of blindness in middle-income countries as well (8, 9). Recognizing this fact, the World Health Organization has identified ROP as a leading cause of vision impairment in children in the developing world (10).

There appear to be a variety of factors that may account for development of ROP, prenatal as well as postnatal. Several complex factors and an association of these elements, i. e. premature nerve tissue contributing to the perverse signal transmission, fragile bronchioles concerning perverted or insufficient gas supply to the eye and retina, vessels expanded reaction to internal or external environment stimuli may be responsible for the development of ROP and subsequent significant long-term visual problems. Alongside birth weight and GA, these factors include mechanical ventilation, elevated blood carbon dioxide levels, exposure of premature retina to a high concentration of oxygen, leading to vasoobliteration followed by vasoproliferation, previously was thought to be the major contributory factor in the development of ROP (11–13). However, reports have found ROP in association with anemia, blood transfusions, intraventricular hemorrhage, respiratory distress syndrome, chronic hypoxia *in utero*, multiple spells of apnea or bradycardia and seizures; exposure to bright fluorescent lighting in hospitals contributes to the development of ROP (14–16). It is also well known that a portion (10%) of very low birth weight premature babies develop advanced ROP (17).

The current thinking is that probably it is a combination of factors, some occurring *in utero* and some after the baby is born, that lead to ROP and blindness. In clinical practice aiming to minimize the blindness for ROP, premature neonate screening and its modifications depending on the demographic index have been introduced. At the Centre of Neonatology of Vilnius University Children's Hospital, the premature neonate electronic database was designed and electronic ROP protocols were compiled considering the effects of prenatal ant postnatal risk factors and their combinations on ROP existence and development. Elucidation of a correlation of risk factors and ROP stage for a particular neonate might contribute to individualized and adequate ROP treatment which can substantially reduce the rate of unfavorable ROP outcomes. Thus, the goal of our research was to combine the optimal clinical and epidemiological markers for developing a ROP risk detection tool. The tool realized an optimal synergy between artificial neural networks and a biosubject, with the purpose to decrease visual disability and blindness from ROP.

MATERIALS AND METHODS

The retrospective observational research of premature neonates was carried out at the Neonatology Centre of Vilnius University Children's Hospital. The research combined examination of epidemiological and clinical characteristics of premature neonates admitted to the neonatology clinic and analysis of ROP protocols throughout the year 2005. Premature infants managed from January 1, 2005 to December 3, 2005, who met the established criteria for ROP screening were eligible for the study.

Eye examinations were performed in all infants who met the criteria set by the Royal College of Ophthalmologists' Guidelines (18, 19). Data were recorded retrospectively, and the presence of retinopathy was graded following the International Classification of ROP and by protocols adapted by Bagdoniene and Sirtautiene to the Lithuanian demographical situation (18, 20). The threshold for treatment followed the protocol derived by Bagdoniene and Sirtautiene (20–22).

The demographical data included gestational age (GA), birth weight (BW), gender, maternal age. Clinical data on neonates included Apgar scores at 1 minute and 5 minutes, umbilical cord (UC) pH, antibiotics and surfactant given, concomitant neonate pathologies (pneumothorax, pulmonary haemorrhage, respiratory distress syndrome, patent ductus arteriosus, neonatal jaundice requiring phototherapy, blood culture-positive septicaemia, intraventricular haemorrhage). The respiratory data included the type of respiratory support, duration on oxygen. Maternal clinical data comprised pregnancy risk factors (anemia, diabetes mellitus and infection) and delivery risk elements (bleeding, preeclampsia, hypertension).

Aiming to determine whether the incidence of ROP was increased at specific exposure levels, the multifactorial risk environment for ROP pathological process was modelled. The variables were grouped continuously: gestational age: less or equal 25; 26–27; 28–31; more or equal 32 weeks; birth weight: 500–999; 1000–1499; 1500–1999; >2000 g; Apgar score: 8–10; 7; 4–6; 0–3; umbilical cord pH (E. Salling's classification): pH >7.25; 7.21–7.25; 7.16–7.20; 7.11–7.15; 7.01–7.10; < 7.01. Duration of ventilation: 1, 2, 3 weeks, exposure to antibiotics: no, 1, 2 and 3 weeks.

Statistical analysis was performed using the Statistical Package For Social Sciences (SPSS) and STATISTICA

programs. Statistical analysis provided that all statistical values were taken into consideration for a particular neonate. Comparison procedures were performed including groups equalization for error minimization purposes, i. e. ROP-nonaffected premature infants were randomly selected into the double major control group and the ROP-affected neonates comprised the case group. Univariate comparison of risk factors between the groups were performed applying statistical modules (cluster analysis, Studen's t test; Pearson's correlation coefficient; linear regression analysis. P values less than 0.05 were considered as statistically significant. Classification is a very important aspect in decision-making; the possibilities of optimal decision based on a series of biomedical data were experimentally shown in previous paper by authors (23). To assess the relative risk of ROP development for a particular premature neonate, for the first time the artificial neural networks were applied, i.e. the purpose of classification we distributed premature neonates into high, moderate or low risk groups of ROP development, depending on the particular neonate's risk factor environment.

RESULTS

During the study period, the Centre of Neonatology managed a total of 256 premature infants. Cases that matched the selection criteria where enrolled into the study. Retinopathy of prematurity was present in 43 (17%) of all of premature neonates. One third of ROP cases underwent surgical treatment.

Maternal factors and demographic features influencing ROP development are presented in Table 1. Multiple births and antepartum hemorrhage were significantly different among mothers whose infants developed any stage of ROP and those who had not ($p < 0.01$). 10% of infants without ROP were born to mothers with preeclampsia, while all infants with ROP requiring surgery were born to mothers without preeclampsia ($p < 0.0001$). Vaginal delivery rate was higher in the group without ROP compared to the ROP group requiring surgery ($p = 0.03$). A lower rate of vaginal delivery in the ROP group probably reflects the high-risk perinatal status of these premature infants at the time of their delivery. The antenatal surfactant and antibiotic usage was not significant in decreasing the severity of ROP. Delivery and pregnancy failure contribute to a higher ROP pattern, as the subsequent infections and bleeding during delivery are the leading pathological status elevating ROP stage.

Clinical features and demographic characteristics of premature neonates are shown in Table 2. The female-to-male ratio of infants with threshold ROP was 1:1. The ratio was 1.2:1 in the group without ROP. The mean gestational age of ROP-affected premature neonates was 28.1 ± 0.9 weeks (range, 25–35 weeks) and the mean birth weight was 1250 ± 214 g (range, 780–2250 g), while in neonates without ROP the mean gestational age was 33.1 ± 0.9 weeks and the mean birth weight 1958 ± 416 g ($p < 0.01$; $p < 0.05$). Infants at the greatest risk of ROP were 1500 g or less at birth ($p < 0.001$) and of 30 weeks of gestational age or younger ($p < 0.05$). An inverse relationship existed between the incidence and severity of ROP and birth weight and gestational age ($r_1 = -0.8$; $r_2 = -0.7$; $p < 0.01$). Infants with ROP had lower 1 minute and 5 minute Apgar scores as compared with infants without ROP ($p < 0.05$). Low Apgar scale rates were positively associated with ROP severity and thus with a high ROP risk level ($r_3 = 0,9$; $p < 0.001$). Higher ROP stages fall to the interval between 7.16–7.20 upon E. Saling scoring, both in ROP neonates requiring and not requiring surgical treatment ($p < 0.05$).

Oxygen therapy had been applied in all ROP stages. Infants with ROP had a higher incidence of respiratory distress syndrome, patent ductus arteriosus requiring indo-methacin or ligation ($p < 0.001$). Infants who developed severe ROP also developed more septicaemia ($p < 0.01$), intraventricular haemorrhage ($p < 0.0001$), neonatal seizures ($p < 0.05$). The incidence of neonatal jaundice was statistically different in the group with ROP and the group with ROP requiring surgery ($p > 0.05$). Concomitant neonate pathologies range within a moderate to high risk level for ROP development, while infant heart and vascular pathologies overpass the high risk level for ROP development ($p < 0.001$).

In an individualized ROP risk detection tool, the main domain is an apropos design of the environment of features influencing the development of ROP. Some of

Table 1. **Maternal factors in premature neonates**

Variable	*No ROP*	*ROP without surgery*	*ROP with surgery*	*Significance*
Maternal age	27 ± 7	28 ± 9	30 ± 6	p > 0.05
Maternal anemia	33%	23%	10%	p > 0.05
Maternal infection	17%	31%	52%	p < 0.05
Antepartum hemorrhage	13%	10%	18%	p < 0.01
Multiple births	17%	4%	33%	p>0.01

Table 2. **Clinical characteristics comparison of premature infants**

Variable	*No ROP*	*ROP without surgery*	*ROP with surgery*
Apgar 1	8 ± 1.0	7 ± 1.0	6 ± 1.2
Apgar 5	9 ± 0.8	8 ± 0.8	7 ± 0.9
UC pH	7.67 ± 0.09	7.27 ± 0.08	7.31 ± 0.05
Birth weigh	1958.2 ± 468.7	1385.5 ± 438,8	1042.5 ± 248.7
Gestational age	33.1 ± 2.2	28.9 ± 2.8	26.82 ± 1,2

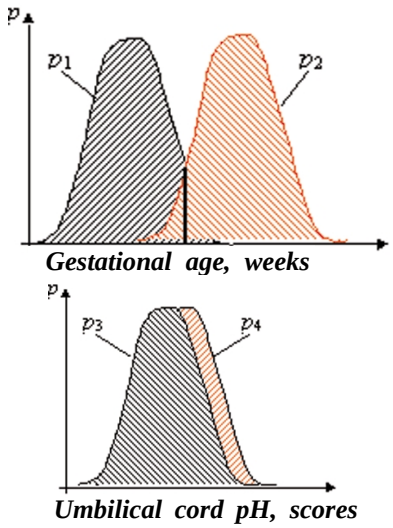

Fig. 1. Gaussian probability density functions for ROP classification

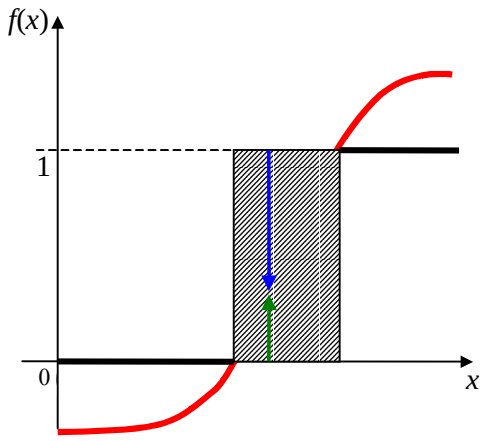

Fig. 2. ROP risk evaluation applying SVM approximated feature space

the characteristics are not specific to ROP, although contribute to it. Retrieval of specific features is the long-lasting and costly process. Though, the main importance falls on identification of particular features whose quantitative expression and interrelation define the risk of ROP for a particular infant. Premature neonate features spread in the Gaussian distribution. A characteristic distribution of premature neonates affected and not affected by ROP is presented in Fig. 1 when the analyzed features are gestational age and umbilical cord pH. The neonate is healthy (black) or ROP-affected (red), and the overlapping reflects the specificity of ROP development. Gestational age is the apropos feature for ROP risk defining ($p < 0.05$), while low UC pH is the apropos feature for prematurity, however, ROP is not associated with this status ($p = 0.8$).

Referring to the statistical analysis of epidemiological and clinical characteristics, the basic factors of ROP are low birth weight and gestational age, low Apgar scale scores, oxygen therapy. The above factors comprise the vector of features applied for classification purposes, i. e. whether or not a particular premature infant is on the risk of developing ROP. Artificial neural networks are advanced techniques for classification multi-dimensional vector purposes. The support vector machine (SVM) algorithm is a classification algorithm that provides state-of-the-art performance in a wide variety of application domains. During the past three years, SVMs have been applied very broadly within the field of computational biology, for classification purposes. Furthermore, we also use this representation of automatical approach of classification for ROP persistence using a machine learning classifier. Applying mapping Φ, $\Phi : R^d \rightarrow H$, the SVM converts one space R^d to another Euclidean space H, where d is the quantity of dimensions, i.e. gestational age, birth weight, Apgar 5 score, oxygen therapy. Then the training algorithm depends only on the data through dot products in H. The kernel function K: $K(\mathbf{x}_i, \mathbf{x}_j) = \Phi(\mathbf{x}_i) \cdot \Phi(\mathbf{x}_j)$ is used in the training algorithm. In this project the kernel function is Gaussian. In the test phase, an SVM is used by computing dot products of a given test point **x** with **w**, or more specifically by computing the sign of a particular assertion, while the determined s_i is the support vector. The pair $\{H, \Phi\}$ exists for the particular kernel K when Mercer's condition is satisfied.

Applying the sorting of SVM training/test sets according to weight values in ascending order, features were selected employing the checkerboard feature selection algorithm, i. e. two experiments were provided with the enlisted epsilon and kernel option sets. The Minkovski error function was adapted for SVM error elucidation, i. e. the resulting values are described as a pseudo-probability-density function evaluating the performance of the SVM. Fig. 2 presents ROP risk evaluation applying an SVM approximated feature space, while SVM approximated feature space (red curve), particular ROP risk evaluation (green and blue arrows) and SVM's intermediate space (hatched rectangle) and risk bound with particular probability vary [0;1]. The overall data set consists of 101 data, the optimal kernel option is 200, and the epsilon is equal to 1e-6. On the SVM basis, an automatic tool for ROP risk evaluation for premature neonates was created.

DISCUSSION

Retinopathy of prematurity continues to be an important cause of potentially preventable blindness worldwide (24). Recent observational studies have found ROP to be a disease of multifactorial origin (25), thus identification of the risk factor environment is of the main importance for a particular neonate. Our research represents a risk factor environment influencing the severity of ROP in Lithuania. Patz et al., in a prospective controlled trial, demonstrated the causal effect of high oxygen administration on the development of ROP (26). However, oxygen therapy is not the only and most important factor of ROP development. The American STOP-ROP trial, which

recruited 649 babies with the mean gestational age of 25.4 weeks, showed that keeping fractational oxygen saturation above 95% slightly reduced the number of babies with pre-threshold ROP who went on to develop disease severe enough to require retinal surgery (27). Ramanthan et al. conclude that physiological low oxygen protocol combined with strict control of fluctuations in oxygen saturation significantly reduces the risk of threshold ROP in VLBW infants (13). ROP might be defined as oxidative stress in the newborn. The pathogenesis of oxygen radical disease of the newborn is clearly presented in a 30-year perspective study by Ola Didrik Saugstad (28). Oxygen is a product capable of doing great harm as well as good, though oxygen therapy needs optimized usage (29), especially for ROP-suspected preterm neonates.

The pathogenesis of the development of ROP is still uncertain. The analysis of risk factors for ROP will help to understand and predict ROP development in high-risk neonates. Low birth weight and young gestational age are the most important risk factors in the development of ROP. Shah et al., after a retrospective study of VLBW infants managed by the department for over 14 years, arrived to the conclusion that the main risk factors for development of ROP are extremely low birth weight (BW < 1000 g), extreme prematurity (GA <3 0 weeks), severe HMD with a longer duration of mechanical ventilation, and supplemental oxygen therapy (30). Chang-Sue Yang et al. also support our research results concluding that the birth weight and gestational age are the most important risk factors in the development of ROP and also the best indicators of immaturity in premature infants. In the current study, the multiple birth itself is not a risk factor of ROP development; as proved by Chang-Sue Yang et al., it is a coexistence of low birth weight and gestational age that is even more important (31). However, in perspective the mentioned risk factor needs elucidation among premature infants. Several other risk factors such as respiratory distress syndrome, patent ductus arteriosus were found to correlate with the development of ROP in our research. Respiratory distress syndrome and chronic lung disease were determined to associate with systemic hypoxia, which will lead to retina ischemia while observing premature infants with birth weight less than 2000 g or gestational age less than 36 weeks (31).

ROP is overlooked on the genetic basis as well. Lois E.H. Smith determined that IGF-1 levels are deficient after premature birth, thus restoration of IGF-1 to levels found *in utero* may help prevent ROP (32). As far as ROP pathogenesis is uncertain, evaluation of the risk factor environment and its qualitative as well as quantitative expression is the basic aim in determining ROP risk for a particular premature infant. In our research, we have proved that the main factors significantly influencing ROP severity are gestational age, birth weight, Apgar score and oxygen therapy. The SVM-based automatic tool objectively describes the risk for ROP development for a particular premature neonate depending on a unique environment of risk features. The proposed tool is an intermediate link between terminal diagnostic processes. In the near perspective, individualized treatment schemes will be defined depending on the neonates' bioparameter environment, and the objective ROP screening protocols will be corrected optimizing the ROP frequency.

CONCLUSIONS

Our study is a comprehensive study evaluating an association of the risk factor environment with ROP severity. ROP protocols should comprise a more detailed analysis of the main risk factors influencing the variance of ROP severity, i.e. O_2 therapy, delivery and pregnancy failure.

Our tool, based on artificial neural networks, has the potentiality to identify the risk level for ROP development with a high sensitivity considering the positive and negative predictive values for a particular immature infant. In perspective, this integrated approach could serve as a basis for compiling a targeted treatment scheme for particular premature neonates.

Received 5 June 2006
Accepted 31 July 2006

References

1. Basys V, Drazdiene N,. Vezbergiene N, Lauzikiene D. Data of medical birth register 2004. Vilnius: Lithuanian Health Information Centre, 2005.
2. Drazdiene N.Pediatrija prasideda nuo naujagimio. Pediatrija 2004; ISSN 1648-4630: 42–46.
3. Nissenkorn I, Wijsenbeek Y, Cohen S. Etiology of blindness in children in Israel in recent years. Acta XXV Council Ophthalmol 1987; 25: 742–4.
4. Steinkuller PG, Du L, Gilbert C, Foster A, Collins ML, Coats DK. Childhood blindness. J AAPOS 1999; 3: 26–32.
5. Goggin M, O'Keefe M. Childhood blindness in the Republic of Ireland; a national survey. Br J Ophthalmol 1991; 75: 425–49.
6. Fleck BW, Dangata Y. Causes of visual handicap in the Royal Blind School, Edinburgh, 1991–2. Br J Ophthalmol 1994; 78: 421.
7. Gibson DL, Sheps SB, Schechter MT, Wiggins S, McCormick AQ. Retinopathy of prematurity: a new epidemic? Pediatrics 1989; 83: 486–92.
8. Gilbert C, Fielder A, Gordillo L et al. 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: 518–22.
9. Gilbert C, Rahi J, Eckstein M, et al. Retinopathy of prematurity in middle-income countries. Lancet 1997; 350: 12–4.

10. WHO's mission for vision. Afr Health 1998; 20: 38.
11. Saugstad O D. Is oxygen more toxic than currently believed? Pediatrics 2001; 108: 1–6.
12. Penn JS, Henry MM, Tolman BL. The range of paO_2 variation determines the oxygen-induced retinopathy in newborn rats. Invest Ophthalmol Vis Sci 1995; 2063–70.
13. Ramanthan R et al. A physiologic low oxygen protocol significantly reduces the incidence of threshold retinopathy of prematurity in very low birth weight premature infants. Abstract 21st workshop on surfactant replacement, Oslo, June 1–4, 2006. Biol Neonate 2006; 89: 348.
14. Glass P, Avery GB, Subramanian KN, Keys MP, Sostek AM, Friendly DS: Effect of bright light in the hospital nursery on the incidence of retinopathy of prematurity. N Engl J Med 1985, 313: 401–4.
15. Brooks SE, Marcus DM, Gillis D, Pirie E, Johnson MH, Bhatia J. The effect of blood transfusion protocol on retinopathy of prematurity: A prospective, randomized study. Pediatrics 1999; 104: 514–8.
16. Kim TI, Sohn J, Pi SY, Yoon YH. Postnatal risk factors of retinopathy of prematurity. Paediatr Perinat Epidemiol 2004, 18: 130–4.
17. Prevent Blindness in Premature Babies Homepage, 1997. Madison, Wisconsin.
18. Report of a joint working party. Retinopathy of prematurity: guidelines for screening and treatment. London: Royal College of Ophthalmology and British Association of Perinatal Medicine, 1995.
19. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. An International Classification of Retinopathy of Prematurity. II. The classification of retinal detachment. Arch Ophthalmol 1987; 105: 906–12.
20. Bagdonienė R, Sirtautienė R. Neišnešiotų naujagimių retinopatija (metodinės rekomendacijos). Vilnius: ISBN 9986-9257-1-1, LR SAM Perinatologijos programa, 1998.
21. Bagdoniene R, Sirtautiene R. Retinopathy of prematurity: modified treatment modality for Zone II disease. Acta medica Lituanica 2005; 12 (2): 37–41.
22. Bagdoniene R, Sirtautiene R. Retinopathy of prematurity. Vilnius: Gilija; 1998.
23. Ustinovichius L, Balcevich R, Kochin D, Sliesoraityte I. The use of verbal classification for determining the course of medical treatment by medicinal herbs. AAIME 2005, LNAI 3581: 276–285.
24. Clemett R, Darlow B. Results of screening low-birth-weight infants for retinopathy of prematurity. Curr Opin Ophthalmol 1999; 10: 155–63.
25. Kinsey VE, Arnold HJ, Kalina RE, Stern L, Stahlman M, Odell G et al. PaO_2 level and retrolental fibroplasia. Pediatrics 1977; 60: 655–68.
26. Patz A, Hoeck LE, De La Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia: nursery observations. Am J Ophthalmol 1952; 35: 1248–53.
27. The Stop ROP Multicentre Study Groups: Supplemental therapeutic oxygen, controlled trial. Pediatrics 2000; 105: 295–310.
28. Saugstad OD. Oxidative stress in the newborn – a 30-year perspective. Biol Neonate 2005; 88: 228–36.
29. Tin W. Oxygen therapy in preterm babies: fifty years of uncertainty. Biol Neonate 2005; 88: 263–64.
30. Shah VA et al. Incidence, risk factors of ROP among VLBW infants in Singapore. Ann Acad Med Singapore 2005; 34: 169–78.
31. Chagn-sue Yang et al. Retinopathy of prematurity: Screening, incidence and risk factors analysis. Chinese Medical Journal (Taipei) 2001; 64: 706–12.
32. Smith L E H. IGF-1 and retinopathy of prematurity in the preterm infant. Biol Neonate 2005; 88: 237–44.