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# Low gestational age and chronic lung disease are synergistic risk factors for retinopathy of prematurity

Vasileios Giapros [a,*], Aikaterini Drougia [a], Ioannis Asproudis [b], Paraskevi Theocharis [a], Styliani Andronikou [a]

[a] Neonatal Intensive Care Unit, University Hospital of Ioannina, Ioannina, Greece
[b] Ophthalmology Department, University Hospital of Ioannina, Ioannina, Greece

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ABSTRACT

*Aims:* This retrospective, population based study was designed to investigate risk factors for development of retinopathy of prematurity (ROP) and their possible interrelationships, in neonates of gestational age (GA) <32 weeks born in a well-defined geographical region.

*Study design—subjects:* The study population included all preterm infants born alive with GA 24–32 weeks in Northwestern Greece during a 9-year period and hospitalised in the regional neonatal intensive care unit (NICU).

*Outcome measurements:* The association was assessed of the presence of ROP with maternal factors: age, pathology of pregnancy, in-vitro fertilisation, multiple gestation, mode of delivery, perinatal factors: gender, antenatal steroids, transportation, resuscitation, GA, birth weight (BW), small for GA status and postnatal morbidity: chronic lung disease (CLD), intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), maximum $O_2$ needs, hypoxic/hyperoxic episodes, patent ductus arteriosus (PDA), sepsis, using multiple logistic regression analysis.

*Results:* Of 189 infants without congenital anomalies born at GA 24–32 weeks ROP was diagnosed in 24 (12.7%) (>grade 2: 6). Logistic regression analysis showed ROP to be strongly associated with GA, odds ratio (OR) 2.1, confidence interval (CI) 1.3–3.3, $p<0.01$ and CLD, OR 10.2, CI 2.3–44, $p<0.01$, respectively, independent of confounding factors. By estimating interaction on an additive scale it was shown that the combined risk effect of GA and CLD was larger than the sum of the individual risk effects, implying synergistic effect.

*Conclusions:* ROP was closely and independently related to both low GA and the diagnosis of CLD, which were interrelated in the development of ROP.



## 1. Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina and it is a major factor of morbidity especially in neonates with extremely low birth weight (LBW). It may lead to visual impairment and even blindness in the affected eye. The increased survival of extremely LBW infants due to recent advances in neonatal care has produced a new population of infants at very high risk of developing ROP [1] and some studies report a rise in the incidence of ROP [2] although others find no such increase [3,4].

The development of ROP has been related to oxygen administration and both hypoxia and hyperoxia have been implicated, as well as abrupt fluctuations in the oxygen ($O_2$) saturation level [5–7]. Its aetiology appears to be multi-factorial and several risk factors other than $O_2$ have been identified, amongst which low gestational age (GA) and LBW appear to play a crucial role. Other probable risk factors which have been identified are male gender [8], maternal age [9], intrauterine growth restriction (IUGR) [8,10], prolonged postnatal steroid treatment [1,11], dependence on ventilation [1], anaemia [12], apnoea [12], hypoxic ischaemic encephalopathy [12], elevated levels of serum iron and blood transfusion [13,14], erythropoietin use [15], microbial [7] or fungal sepsis [16–18], hyperglycaemia [19], vaginal delivery [20] and genetic background [21].

These risk factors for ROP found in the various studies may be true predictors but may be a reflection of the overall severity of the clinical condition of the neonate. They were not all identified in all the pertinent studies, and their clinical value remains questionable [17,22]. Very few studies examined the interrelationship of the various independent risk factors in the development of ROP [7], which could offer useful information regarding precise risk estimation and help in planning risk reduction intervention.

This retrospective, population based study was designed to investigate risk factors for development of ROP and their possible interrelationships in neonates of GA<32 weeks born in a well-defined geographical region and hospitalised in the regional neonatal intensive care unit (NICU).

* Corresponding author at: University Hospital of Ioannina, P.O. Box 1186, Ioannina 451 10, Greece. Tel.: +30 2651007544; fax: +30 2651007038.
*E-mail address:* vgiapros@cc.uoi.gr (V. Giapros).

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## 2. Patients and methods

The retrospective study took place in the University Hospital of Ioannina, the regional hospital that accommodates the majority of deliveries (>80%) in a well-defined area in Northwest Greece. The NICU of this hospital is the referral centre for the region of Northwest Greece and all preterm neonates with GA<34 weeks born elsewhere in the region are transported to the unit immediately after birth. The study aimed to include all preterm neonates born with a GA of 24–32 weeks or BW <1500 g and hospitalised in the NICU during the 9-year period 1/1/2000 to 31/12/2008. The parents of all the infants eligible to participate in the study were contacted and their written permission to use data from their children's case notes was elicited. The Ethics Committee of the Hospital approved the study protocol. Neonates with congenital anomalies were excluded from the study.

The primary clinical outcomes studied were the development of any stage of ROP, and the development of ROP severe enough to require therapeutic intervention. Additional outcome measures included comorbidities and the characteristics of the clinical course of the neonates in the NICU, which are listed in Table 2. ROP was graded according the Committee for the Classification of Retinopathy of Prematurity [23]. All assessments for ROP were made by the same paediatric ophthalmologist throughout the study period. Ophthalmological examination started at 4 weeks after delivery in neonates with GA 27–32 weeks and at 6 weeks in neonates with GA<27 weeks. Follow-up examinations were made until the resolution of ROP or until retinal maturation, on a weekly basis or even more frequently, based on the finding at the previous examination. The study infants then had regular eye examinations up to preschool age, conducted by the same paediatric ophthalmologist. The treatment criteria were based on the guidelines set by Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) revised later (2005 onwards) by those set by the Early Treatment of Retinopathy of Prematurity (ET-ROP) study [24,25]. The GA was calculated by early ultrasonography (US) performed at 8–16 weeks GA. When an early US was not available the date of the last menstrual period combined with clinical assessment after birth based on a modified Ballard score – to include extremely preterm neonates – was used to estimate the GA [26].

A range of maternal, pregnancy and perinatal factors were investigated. All the pertinent information was entered in the electronic database by one of the authors (AD) consistently throughout the study period. The routine paper medical records of all study neonates were also available for cross-checking, and cross-checks with other departments (e.g., microbiology, ophthalmology) were made when necessary. The maternal and pregnancy factors considered included: maternal age; in-vitro fertilisation (IVF); hypertensive disease of pregnancy, defined as maternal blood pressure>140 mm Hg systolic and >90 mm Hg diastolic, accompanied by proteinuria; antenatal steroid administration (AS), (a full course at least 24 h before delivery); mode of delivery; prolonged rupture of membranes (PROM), defined as leakage of amniotic fluid for more than 18 h before delivery; clinically diagnosed chorioamnionitis, multiple gestation, 3rd trimester haemorrhage and gestational diabetes mellitus. The perinatal variables studied were: GA; BW; gender; need for transportation from another area; need for resuscitation at birth, small for gestational age (SGA) status, examined either as BW<10th and BW<3rd percentile in the Alexander growth charts [27]; intraventricular haemorrhage (IVH), based on weekly US evaluation starting in the first week of life, according to Papile criteria [28]; haemodynamically significant patent ductus arteriosus (PDA) diagnosed clinically and confirmed and graded by US; necrotizing enterocolitis (NEC), based on modified Bell's criteria [29]; sepsis, diagnosed by a positive blood culture and compatible signs and symptoms; respiratory distress syndrome (RDS), based on clinical and radiological criteria; maximum $O_2$ needs, need for and duration of mechanical ventilation (MV), chronic lung disease (CLD), based on oxygen need at or beyond 36 weeks postmenstrual age (PMA = GA plus postnatal age in weeks) [30], hyperoxic/hypoxic episodes, defined as the sum of reported events of arterial $O_2$ saturation >95% before 32 weeks and <85% after 32 weeks PMA estimated by pulse oximeter, (as ROP may triggered by hyperoxia early and by hypoxia late in its course) [31], postnatal steroid administration, and duration of hospitalisation.

The main hospital protocols in use during the study period included those for antenatal steroid administration, early surfactant treatment, use of several modalities of ventilation: nCPAP, SIMV or AC combined with Pressure Support (PS), High Frequency Oscillation (HFV) as rescue treatment, administration of xanthines in the periextubation period and early brain scans. The $O_2$ saturation target range was 88–93% with alarm limits set at 85 and 95%. In addition there was a restricted policy for blood transfusion, antibiotic use and postnatal steroids and strict protocols regarding early enteral trophic feeding and early high protein administration in parenteral fluids, and a breastfeeding protocol. As the neonatal services in the catchment area are strictly regionalized >95% of preterm infants continue the hospital follow-up programme up to 2 years of age. The regional perinatal and neonatal mortality rates have been recently reported [32].

During the 9-year study period the more important changes in the management of preterm neonates were in the use of ventilation modalities (PS, hybrid pressure–volume modes) and protocols aiming to a gentle ventilation principle, and also efforts for reduction in administration of antibiotics. Other major changes, such as increased antenatal steroid use and higher rates of in-utero transportation had already been implemented by the start of the study period [32].

## 3. Statistical analysis

Comparison of the outcomes of the study infants, examining either the entire cohort or its GA sub-categories, was made using Fisher's exact and $x^2$ tests for categorical values and Students t-test for continuous variables. Fisher's exact test was used instead of $x^2$ test when cell frequencies were less than 5. Multiple logistic regression analysis was used to establish whether the observed statistical differences between the two groups with or without ROP were independent of confounding factors. Continuous variables were not dichotomized in the main regression analysis. The results are presented as odds ratios (OR) plus confidence intervals (CI). In each regression the confounders used were those factors that, based on clinical experience or other studies, could possibly affect the relation of the dependent variable (ROP) to the outcome variables. The interactions between those independent variables, which were found to relate significantly with the development of ROP, were examined by using a $2\times2$ table and the Relative Excess Risk due to Interaction (RERI) which is another measure for interaction as departure from additivity, was calculated [33]. A p level of 0.05 was regarded as statistically significant. Statistical analyses were performed using the StatView software package of SAS Institute Inc. (Cary, NC, US).

## 4. Results

Amongst the 247 preterm neonates with GA≤32 weeks or BW≤1500 g hospitalised during this period, 201 (81.4%) survived until discharge and were eligible for inclusion in the study. These 247 neonates with GA 24–32 weeks that were hospitalised in the NICU during the 9-year study period, represent 5.84% of all hospitalised neonates (n = 4228) and 1.04% of the 23,740 live births in the region during the study period. Twelve neonates were excluded due to lack of adequate information on their perinatal history and the remaining 189 comprised the study population. In all but 15 cases GA was based on early US scan. Amongst the study group, ROP was diagnosed in