

## Risk factors for retinopathy of prematurity: a systematic review

Fatores de risco para retinopatia da prematuridade: uma revisão sistemática

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## ABSTRACT

To describe the prevalence of risk factors for retinopathy of prematurity and respective stages. Retrospective data were extracted from original articles addressing risk factors for retinopathy of prematurity retrieved from Scientific Electronic Library Online (SciELO), Virtual Health Library (VHL) and National Library of Medicine - NLM (PubMed) databases. In the initial search, 186 articles were found. Following title and abstract reading and application of inclusion and exclusion criteria, 25 articles were selected for this analysis. Variables of interest varied widely between studies. Gestational age and birth weight were listed as risk factors in all studies. Gender analysis revealed small gender-related differences, since approximately 52.9% of affected neonates were males and 47.1% females. As to race/color, approximately 72.7% were white, 12% were brown and 2.7% were black. However, there is a lack of consensus over the significance of these factors. The study revealed that retinopathy of prematurity is a multifactorial disease primarily associated with prematurity, low birth weight and oxygen therapy. Albeit potentially avoidable and reversible, the incidence of the condition is high. Therefore, further studies along the same lines are needed for deeper understanding of risk factors for or retinopathy of prematurity and mitigation of long-term consequences.

## RESUMO

O objetivo deste estudo foi descrever a prevalência dos fatores de risco associados à retinopatia da prematuridade e aos seus estágios. Para isso, foi realizado uma busca nas bases de dados SciELO, VHL e PubMed® de estudos originais que analisavam os fatores de risco para retinopatia da prematuridade foram encontrados. Inicialmente, encontrou-se 186 artigos. Após a leitura dos títulos e dos resumos e de acordo com os critérios de inclusão e de exclusão, foram escolhidos 25 artigos para compor a base de dados deste estudo. Observa-se que houve uma grande diversidade nas variáveis dos estudos. Em relação aos fatores de risco, todos os artigos mencionaram idade gestacional e peso. Ao analisar o sexo, houve uma pequena discrepância, cerca de 52,9% eram do sexo masculino e 47,1% do feminino. Em relação à raça/cor, aproximadamente 72,7% eram brancos, 12% pardos e 2,7% pretos. No entanto, não há consenso sobre esses aspectos na literatura. O estudo constatou que a retinopatia da prematuridade é uma doença multifatorial, tendo como principais fatores de risco prematuridade, baixo peso ao nascer e oxigenoterapia. Trata-se de uma doença de alta incidência, apesar de ser evitável e reversível, portanto, pesquisas como esta são essenciais para conhecer os fatores associados e, assim, reduzir as consequências a longo prazo da doença.

## INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative ocular disease caused by inappropriate vascularization of the immature retina of preterm newborns (PTNB).<sup>(1)</sup> The condition was first described by Terry<sup>(2)</sup> in 1942 and named retrolental fibroplasia. In 1949, Owens and Owens observed the disease could also occur in the postnatal period and, in 1951, Campbell suggested oxygen therapy might be a significant triggering factor.<sup>(3,4)</sup>

Retinopathy of prematurity is a potentially avoidable cause of blindness in children. Approximately 50,000 new cases of ROP are diagnosed annually, primarily in Latin America newborns.<sup>(1)</sup> In Brazil, 16,000 PTNBs are estimated to develop ROP each year and approximately 10% of these cases progress to blindness when left untreated.<sup>(5)</sup> Recent studies indicate a growing number of cases of ROP. This may reflect larger numbers of premature births, financial constraints, delayed referral or unpreparedness of many ophthalmologists and resultant misdiagnosis and lack of appropriate treatment.<sup>(1,6)</sup>

Also important, ROP is a multifactorial disease which may involve the following risk factors: oxygen therapy, intracranial hemorrhage, maternal factors such as multiple pregnancies, diabetes mellitus, advanced maternal age, smoking, iron deficiency, placental detachment and maternal preeclampsia, blood transfusions, septicemia, congenital infections, patent ductus arteriosus, Apgar score lower than 7 at five minutes, small stature for gestational age (GA) and especially prematurity and low birth weight (BW).<sup>(7,8)</sup> It is estimated that 66 to 68% of PTNBs weighing less than 1,251 g develop ROP and this percentage rises to 82% in PTNBs weighing less than 1,000 g.<sup>(9)</sup>

The International Classification of Retinopathy of Prematurity (ICROP) defines ROP according to the anteroposterior location of retinopathy (zones I, II and III), circumferential extension (clock hour distribution or 30° sectors), severity of abnormal vascular response (stages 1 to 5) and additional signs of severity such as venous dilatation and retinal artery tortuosity, which indicate more aggressive disease (plus disease). This classification is used for recognition of threshold ROP, which is defined as stage 3 plus disease with more than 5 contiguous or 8 cumulative clock hours of fibrovascular proliferation in zones I and II.<sup>(10)</sup> The clinical significance of threshold ROP lies in the fact that, in the absence of appropriate treatment, approximately 50% of cases will progress to retinal detachment and loss of vision.<sup>(11)</sup>

In order to mitigate long-term consequences, *Sociedade Brasileira de Pediatria* (SBP) recommends

binocular indirect ophthalmoscopy between the 4<sup>th</sup> and 6<sup>th</sup> weeks of life in newborns (NBs) with BW less than 1,501 g and/or GA under or equal to 32 weeks. Respiratory distress syndrome or sepsis, blood transfusions, multiple pregnancies and intraventricular hemorrhage are also indications for binocular indirect ophthalmoscopy, since these are thought to be risk factors for threshold ROP development.<sup>(12)</sup>

The traditional treatment of threshold ROP consists of complete destruction of the avascular retina using transpupillary photocoagulation or transscleral cryotherapy. Cases diagnosed in the initial phase of disease and appropriately treated have 41% less chance of progressing to retinal detachment and 9 to 24% less chance of progressing to blindness within 5 to 15 years. However, in more than 40% of affected children, visual acuity in the treated eye is less than 20/200.<sup>(9,13)</sup>

With regard to the pre-threshold stage of the disease, early treatment is only indicated in type 1 pre-threshold ROP (zone I plus with any stage, zone I stage 3 with no plus and zone II stages 2 or 3 plus). Treatment reduces the risk of severe visual impairment and structural damage from 19.5% to 14.5% and from 15.6% to 9.1% respectively. Still, in spite of laser treatment, affected patients have persistent vascular activity and rates of progression to retinal detachment are high. In patients with type 2 pre-threshold ROP (zone I stage 1 or 2 with no plus or zone II stage 3 with no plus) treatment is not recommended, since spontaneous regression is expected in 52% of cases. However, these cases may progress to type 1 disease and must therefore be closely monitored.<sup>(13)</sup>

Given ROP is clinically significant and a public health concern, this review set out to describe the prevalence of risk factors for the condition and respective stages.

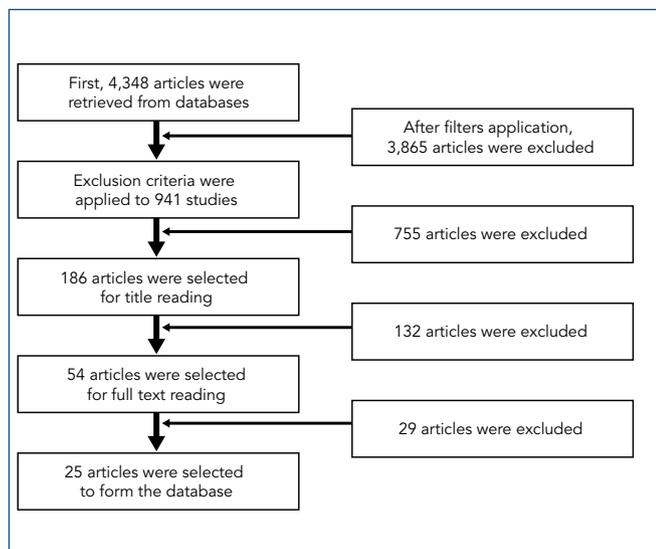
## METHODS

This systematic review stemmed from a quantitative, retrospective and documentary research addressing ROP in Brazil. Articles published between 2010 and 2020 were used. Importantly, systematic reviews are defined as secondary studies based on data extracted from primary studies.

The Scientific Electronic Library Online (SciELO), the Virtual Health Library (VHL) and the National Library of Medicine (NLM; PubMed®) databases were searched using the search terms “retinopathy”, “prematurity” and “risk factors”. In order to limit the number of articles retrieved, the Boolean operator “AND” and the following filters were applied: articles published in the last 10

years, studies conducted in Brazil, search terms used in the title or abstract, full text and no language restrictions. Government information, editorials, expert opinions, health guides, Ministry of Health documents, comments, technical and scientific reports were excluded. Articles unrelated to the topic or that did not match the specific purpose of this work were also left out.

A total of 4,348 articles were retrieved in the initial search using the Boolean operator described. Following filter application, 3,407 articles were excluded, and 941 articles retained. Exclusion criteria were then applied, and 86 articles selected for title reading. Of these, 54 articles were extracted for full text reading. The final sample comprised 25 articles, which formed the basis of this analysis (Figure 1).



**Figure 1.** Flow chart showing the article selection process.

Selected articles were reviewed by two independent investigators. In case of mismatches, a third investigator was called upon to determine whether the article in question should be retained in the sample. The Kappa coefficient was used to examine the level of agreement between the investigators - in other words, the ability to measure equal results derived from dependent samples. The kappa coefficient in this study (0.8173) indicated almost perfect agreement (Landis *et al.*).<sup>(14)</sup> Therefore, the analysis was continued (Table 1).

**Table 1.** Kappa coefficient

	Category 1*	Category 2†
Category Kappa	0.8173	0.8173
Standard error of category Kappa	0.0645	0.0636
95% confidence interval for category Kappa	Upper: 0.9438 Lower: 0.6908	Upper: 0.9417 Lower: 0.6929

\*Articles included in the study; †articles excluded from the study

## RESULTS

The number of NBs in articles in this sample totaled 6,897. Only one article (4%) failed to describe the number of patients with or without ROP in a sample of 71 NBs.<sup>(15)</sup> Retinopathy of prematurity affected 2,128 NBs, whereas 4,698 NBs did not develop the disease (30.8% and 67.2% respectively).

Most articles included in this study were published in 2019 (28%), followed by 2010 and 2018 (16% respectively) (Table 2). No articles published between 2014 and 2020 were selected. In this sample, 36% of selected articles were cohort studies and approximately 56% retrospective studies.

**Table 2.** Type of studies and sample size

Author	Sample size (n)	Type of study
Souza <sup>(11)</sup>	50	Prospective descriptive and analytical longitudinal clinical trial for individualized intervention
Rover <i>et al.</i> <sup>(15)</sup>	71	Retrospective study
Portes <i>et al.</i> <sup>(14)</sup>	151	Observational cohort study
Schumann <i>et al.</i> <sup>(17)</sup>	73	Retrospective cross-sectional study
Shinsato <i>et al.</i> <sup>(18)</sup>	70	Prospective study
Tomé <i>et al.</i> <sup>(19)</sup>	148	Retrospective cross-sectional observational study
Almeida <i>et al.</i> <sup>(20)</sup>	33	Retrospective cohort study
Vieira <i>et al.</i> <sup>(21)</sup>	267	Retrospective study
Fortes Filho <i>et al.</i> <sup>(22)</sup>	157	Prospective cohort study
Gonçalves <i>et al.</i> <sup>(23)</sup>	110	Longitudinal study
Jorge <i>et al.</i> <sup>(24)</sup>	232	Prospective cohort study
Moinho <i>et al.</i> <sup>(25)</sup>	343	Observational case-control study
Silva <i>et al.</i> <sup>(26)</sup>	172	Retrospective, analytical, case-control study
Theis <i>et al.</i> <sup>(27)</sup>	320	Cross-sectional and retrospective study
Freitas <sup>(28)</sup>	602	Retrospective cohort study
Horewicz <i>et al.</i> <sup>(29)</sup>	183	Quantitative research approach with descriptive cross-sectional design
Martins <sup>(30)</sup>	280	Observational epidemiological study with case control design
Pereira <i>et al.</i> <sup>(31)</sup>	296	Retrospective cross-sectional study
Fonseca <i>et al.</i> <sup>(32)</sup>	323	Cohort study
Lamy-Filho, <sup>(33)</sup>	1.961	Retrospective cohort study
Malheiro <i>et al.</i> <sup>(34)</sup>	375	Retrospective study
Okamoto <i>et al.</i> <sup>(35)</sup>	58	Cohort study
Pastro <i>et al.</i> <sup>(36)</sup>	181	Retrospective cohort study
Xavier <i>et al.</i> <sup>(37)</sup>	119	Cross-sectional, retrospective study
Cagliari <i>et al.</i> <sup>(38)</sup>	322	Retrospective study

Only two (8%) of the articles in which the sample was divided into patients with or without ROP did not use ICROP disease classification criteria (severity stages 1 to 5).<sup>(31,32)</sup> All articles addressed stages 1 and 3 ROP and only one article<sup>(22)</sup> did not include stage 2 ROP. As to stages 4 and 5, NBs with stage 4 ROP were investigated in ten articles (40%)<sup>(16,21,22,24,25,27,30,32,34,38)</sup> and NBs with stage 5 ROP in eight articles (32%).<sup>(16,21,22,27,30,31,32,38)</sup>

With regard to the number of eyes analyzed and classified according to ROP severity, 4,698 did not have

ROP, 820 had stage 1 disease and 404 had stage 2 disease (68.1%, 11.9% and 5.8% respectively). Remaining eyes were classified as stage 3 (286, 4.1%), stage 4 (28, 0.4%) or stage 4 (25, 0.4%).

Characteristics of NBs described in studies in this sample are shown in table 3. Variables of interest varied widely between studies, with the exception for the GA and the BW, which were addressed all studies. In some studies,<sup>(20)</sup> analysis of variables was limited to NBs with ROP.

Gender analysis revealed small gender differences, since approximately 52.9% of NBs were male and 47.1% female (1,735 and 1,544 respectively). As to type of pregnancy, approximately 80% were single and 20% multiple

(1,656 and 425 respectively). Only four studies contained prenatal care information. In those studies, approximately 73.6%,<sup>(23)</sup> 83.6%,<sup>(17)</sup> 89%<sup>(32)</sup> and 92.3%<sup>(33)</sup> of pregnancies were followed up. Only two articles<sup>(17,23)</sup> addressed complications during pregnancy or labor. Complication rates in those studies (64.4% and 38.3% respectively) were similar to rates reported by Schumann et al.<sup>(17)</sup>. Race/color data were reported in a single article.<sup>(29)</sup> In that article, approximately 72.7% of NBs were white, 12% were brown and 2.7% were black (133, 22 and 5 respectively). The color/race of remaining NBs (23, 12.6%) was not informed. As to risk factors, GA and BW were mentioned in all studies (Table 4).

**Table 3.** Sample characteristics

Author	Gender (male/female)	Gestational age (weeks)	Birth weight (gram)	Gestation	Mode of delivery	Apgar Score
Souza <sup>(11)</sup>	23/27	<30: 14 30-32: 24 >32: 11 Average: 30.9	<1,000: 12 1,000-1,500: 35 >1,500: 3	Twin: 4 Single: 46	-	-
Rover et al. <sup>(15)</sup>	36/35	Average: 29.4	VLBW AGA: 50 NBs	-	Vaginal: 29 Cesarean: 42	-
Portes et al. <sup>(14)</sup>	-	Average: 26.62	Average: 1,109	-	-	1st minute average: 5.5
Schumann et al. <sup>(17)</sup>	33/40	Average: 30.5	Average: 1,153 SGA: 36	Prenatal care: 61 Intercurrence: 47	Vaginal: 23 Cesarean: 50 Intercurrence: 28	5th minute average: 8
Shinsato et al. <sup>(18)</sup>	-	Average: 28.155	Average: 1,030.935	-	-	1st minute average: 5.2
Tomé et al. <sup>(19)</sup>	-	<28: 8 28-32: 65 31-34: 56 35-36: 17 >36: 3	≤1,000: 27 1,000-1,500: 115 >1,500: 6	-	-	1st minute ≤3: 20 5th minute ≤7: 27
Almeida et al. <sup>(20)</sup>	-	Average: 30.51	Average: 1,182.35	-	-	-
Vieira et al. <sup>(21)</sup>	135/132	Average: 29	Average: 1,193	Twin: 72 Single: 195	Vaginal: 69 Cesarean: 198	-
Fortes Filho et al. <sup>(22)</sup>	65/92	Average: 28.3	Average: 844,04	-	Twin: 22	-
Gonçalves et al. <sup>(23)</sup>	54/56	≤ 32	≤1,500	Prenatal care: 81 Intercurrence: 79	Vaginal: 72 Cesarean: 38	<7 1st minute: 73 5th minute: 26
Jorge et al. <sup>(24)</sup>	118/114	Average: 29.4	Average: 1,219.4	Twin: 39 Single: 193	-	-
Moinho et al. <sup>(25)</sup>	186/157	Average: 29.5	Average: 1,173	Twin: 93 Single: 250 Complicated: 215	-	-
Silva et al. <sup>(26)</sup>	98/74	Average: 29.4	Average: 1,171.9	-	-	1st minute average: 5
Theis et al. <sup>(27)</sup>	-	<32: 194 32-37: 115 >37: 11	<1,000: 54 1,000-2,500: 251 >2,500: 15	Twin: 49 Single: 271	-	-
Freitas <sup>(28)</sup>	302 /300	Average: 29.4	<1,000: 148	Twin: 108 Single: 494	-	1st minute average: 6
Horewicz et al. <sup>(29)</sup>	93/ 90	27-31: 66 32-35: 98 >36: 19	<970: 19 987-1,950: 140 >1,950: 23	-	-	-
Martins <sup>(30)</sup>	132/141	≤27: 55 >27: 224	≤1,000: 88 1,000-1,500: 188	-	-	-
Pereira et al. <sup>(31)</sup>	152/144	Average: 32.08	Average: 1,662.54	Prenatal care: 273	Vaginal: 93 Cesarean: 103	<7 1st minute: 107 5th minute: 30
Fonseca et al. <sup>(32)</sup>	55/45	Average: 28.6	Average: 1,041	Prenatal care: 89	Vaginal: 37 Cesarean: 63	<7 5th minute: 29
Lamy-Filho. <sup>(33)</sup>	-	≤35	≤2,000	-	-	-
Malheiro et al. <sup>(34)</sup>	-	Average: 29.3	Average: 1,158.7	-	-	-
Okamoto et al. <sup>(35)</sup>	26/32	30	Average: 1,061.8	-	-	-
Pastro et al. <sup>(36)</sup>	-	<37	<2,000	-	-	-
Xavier et al. <sup>(37)</sup>	54/65	23-25: 8 26-29: 19 30-32: 4 >32: 0	<1,000: 22 1,000-1,499: 6 1,500-2,500: 3 >2,500: 0	-	Vaginal: 73 Cesarean: 46	-
Cagliari et al. <sup>(38)</sup>	173/ 149	Average: 29.5	Average: 1,181.8	-	-	-

VLBW: very low birth weight preterm; AGA: appropriate for gestational age; NB: newborn; SGA: small for gestational age.

**Table 4.** Risk factors for retinopathy of prematurity

Risk factor	Scientific evidence	Lack of scientific evidence	Variable
Gestational age	All	-	Smaller
Birth weight	All	-	Smaller
Oxygen exposure time	Portes et al. <sup>(14)</sup> Schumann et al. <sup>(17)</sup> Shinsato et al. <sup>(18)</sup> Souza <sup>(11)</sup> Tomé et al. <sup>(19)</sup> Almeida et al. <sup>(20)</sup> Vieira et al. <sup>(21)</sup> Moinho et al. <sup>(25)</sup> Silva et al. <sup>(26)</sup> Theis et al. <sup>(27)</sup> Horewicz et al. <sup>(29)</sup> Martins <sup>(30)</sup> Okamoto et al. <sup>(35)</sup> Pastro et al. <sup>(34)</sup> Xavier et al. <sup>(37)</sup> Lamy-Filho. <sup>(33)</sup> Cagliari et al. <sup>(38)</sup> Fortes Filho et al. <sup>(22)*</sup>	-	Longer duration (days)
Type of oxygen exposure	Shinsato et al. <sup>(18)</sup> Tomé et al. <sup>(19)</sup> Moinho et al. <sup>(25)</sup> Lamy-Filho. <sup>(33)</sup> Pastro et al. <sup>(34)</sup> Cagliari et al. <sup>(38)</sup> Fortes Filho et al. <sup>(22)*</sup>	Portes et al. <sup>(14)</sup> Martins <sup>(30)</sup>	Mechanical ventilation CPAP Others
Apgar 1st minute	Portes et al. <sup>(14)</sup> Pereira et al. <sup>(31)</sup> Silva et al. <sup>(26)</sup> Gonçalves et al. <sup>(23)</sup>	-	Changed
Apgar 5th minute	Schumann et al. <sup>(17)</sup> Moinho et al. <sup>(25)</sup> Silva et al. <sup>(26)</sup> Lamy-Filho. <sup>(33)</sup> Gonçalves et al. <sup>(23)</sup>	Portes et al. <sup>(14)</sup> Souza <sup>(11)</sup> Pereira et al. <sup>(31)</sup>	Changed
Sepsis	Moinho et al. <sup>(25)</sup> Theis et al. <sup>(27)</sup> Martins <sup>(30)</sup> Xavier et al. <sup>(37)</sup> Fonseca et al. <sup>(32)</sup> Gonçalves et al. <sup>(23)</sup>	Portes et al. <sup>(14)</sup> Shinsato et al. <sup>(18)</sup> Souza <sup>(11)</sup>	Presence
Comorbidity/respiratory syndromes	Vieira et al. <sup>(21)</sup> Moinho et al. <sup>(25)</sup> Theis et al. <sup>(27)</sup> Freitas <sup>(28)</sup> Lamy-Filho. <sup>(33)</sup> Xavier et al. <sup>(37)</sup> Gonçalves et al. <sup>(23)</sup>	Portes et al. <sup>(14)</sup> Shinsato et al. <sup>(18)</sup> Martins <sup>(30)</sup> Silva et al. <sup>(26)</sup>	Presence
Cardiovascular comorbidity	-	Portes et al. <sup>(14)</sup>	Presence
Digestive comorbidity	-	Silva et al. <sup>(26)</sup> Freitas <sup>(28)</sup>	Presence
Hemodynamic impairment	Vieira et al. <sup>(21)</sup>	-	Presence
Use of surfactant	Vieira et al. <sup>(21)</sup> Moinho et al. <sup>(25)</sup> Silva et al. <sup>(26)</sup> Lamy-Filho. <sup>(33)</sup> Gonçalves et al. <sup>(23)</sup>	Portes et al. <sup>(14)</sup> Martins <sup>(30)</sup> Xavier et al. <sup>(37)</sup>	Higher dose and longer use
Use of aminophylline or caffeine	Gonçalves et al. <sup>(23)</sup>	-	-
Use of indomethacin	Moinho et al. <sup>(25)</sup>	Portes et al. <sup>(14)</sup> Martins <sup>(30)</sup>	Higher dose and longer use
Use of erythropoietin	Vieira et al. <sup>(21)</sup>	-	Higher dose and longer use
Use of diuretic	Shinsato et al. <sup>(18)</sup> Gonçalves et al. <sup>(23)</sup>	Martins <sup>(30)</sup>	Higher dose and longer use
Blood type and RH factor	-	Portes et al. <sup>(14)</sup>	-
Neonatal infections	Theis et al. <sup>(27)</sup>	Portes et al. <sup>(14)</sup> Okamoto et al. <sup>(35)</sup>	Presence
Intraventricular hemorrhage	Vieira et al. <sup>(21)</sup> Theis et al. <sup>(27)</sup> Freitas <sup>(28)</sup>	Souza <sup>(11)</sup>	Presence
Intracranial hemorrhage	-	Shinsato et al. <sup>(18)</sup> Moinho et al. <sup>(25)</sup> Silva et al. <sup>(26)</sup> Martins <sup>(30)</sup>	Presence Moinho et al. <sup>(25)</sup>

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Risk factor	Scientific evidence	Lack of scientific evidence	Variable
Intracranial hypertension	Tomé et al. <sup>(19)</sup>	-	Presence
Phototherapy	Martins <sup>(30)</sup>	-	Longer use
Blood transfusions	Schumann et al. <sup>(17)</sup> Shinsato et al. <sup>(18)</sup> Tomé et al. <sup>(19)</sup> Vieira et al. <sup>(21)</sup> Theis et al. <sup>(27)</sup> Martins <sup>(30)</sup> Lamy-Filho. <sup>(33)</sup> Pastro et al. <sup>(34)</sup> Xavier et al. <sup>(37)</sup> Cagliari et al. <sup>(38)</sup> Gonçalves et al. <sup>(23)</sup>	Souza <sup>(11)</sup> Okamoto et al. <sup>(35)</sup>	Larger number
Gender	-	Souza <sup>(11)</sup> Moinho et al. <sup>(25)</sup> Theis et al. <sup>(27)</sup> Freitas <sup>(28)</sup> Martins <sup>(30)</sup>	-
Mode of delivery	-	Vieira et al. <sup>(21)</sup> Freitas <sup>(28)</sup>	-
Hypoglycemia	-	Okamoto et al. <sup>(35)</sup>	-
Jaundice	Xavier et al. <sup>(37)</sup>	Silva et al. <sup>(26)</sup> Okamoto et al. <sup>(35)</sup>	-
Gestational complications	-	Moinho et al. <sup>(25)</sup> Okamoto et al. <sup>(35)</sup>	Presence
Twin pregnancy	Jorge et al. <sup>(24)</sup>	Souza <sup>(11)</sup> Moinho et al. <sup>(25)</sup> Theis et al. <sup>(27)</sup>	-
Patent ductus arteriosus	Tomé et al. <sup>(19)</sup> Moinho et al. <sup>(25)</sup> Theis et al. <sup>(27)</sup> Xavier et al. <sup>(37)</sup> Fonseca et al. <sup>(32)</sup>	Martins <sup>(30)</sup>	Presence

\* risk factors for severe retinopathy of prematurity.

CPAP: continuous positive airway pressure.

## DISCUSSION

Prematurity is a common cause neonatal disorders due to immaturity. In the majority of cases, preterm babies are born with low weight and require hospitalization and interventions such as oxygen therapy, blood transfusion and neonatal Intensive Care Unit (NICU) procedures.<sup>(39)</sup> Hence the implementation and refinement of neonatal care techniques aimed at enabling the survival of increasingly premature babies. However, these advanced techniques may contribute to the development of ROP, a major cause of visual impairment or blindness in babies born prematurely.<sup>(39,40)</sup>

In this study, the prevalence of retinopathy was approximately 32.3%. Similar prevalence (29.9%) has been reported in prior Brazilian studies.<sup>(41)</sup> Disease classification analysis revealed that most NBs (11.9%) had stage 1 ROP, followed by stages 2, 3, 4 and 5 (5.8%, 4.1%, 0.4% and 0.4% respectively). Likewise, in a Brazilian study by Torigoe,<sup>(40)</sup> 12.17% of newborns had stage 1 ROP, 8.9% progressed to stage 2, 5.04% reached stage 3 and 2.08% developed stage 3 threshold disease, the most severe form of ROP reported during the follow-up period in that study. The high prevalence and severity of ROP emphasizes the need to discuss related risk factors.

Birth weight and GA are inversely related to the incidence of ROP.<sup>(42)</sup> Severe ROP is more common in newborns

born with GA <28 weeks or BW <1,000 g, with few cases reported among newborns with BW over 1,500 g or GA over 32 weeks.<sup>(5)</sup>

In a sample comprising 1,070 NBs examined by Reisner et al.,<sup>(43)</sup> ROP prevalence rates of 21% and 72% were reported in neonates weighing less than 1,500 g and 1,000 g respectively. In turn, the relationship between GA and ROP can be explained by the fact that retinal blood vessels reach the periphery of the nasal retina in the eighth month of pregnancy and the temporal retina at term. Therefore, the preterm peripheral retina is avascular at birth. Following premature birth, normal retinal vascular development is interrupted and part of retinal blood vessels are obliterated.<sup>(39)</sup>

The last classic risk factor for ROP is oxygen therapy, which is strongly related to the etiology of the disease. In preterm neonates submitted to hyperoxia in the first hours or days of life, vascular endothelium growth factor (VEGF) production is inhibited. As a consequence, new blood vessel formation is interrupted and existing vessels are obliterated. Exposure of preterm babies to the natural environment without supplemental oxygen combined with the high metabolic needs of the developing eye create hypoxic conditions in the peripheral retina, triggering large scale VEGF production and leading to the formation of new, but abnormal (i.e., dilated and tortuous) vessels.<sup>(44,45)</sup> Oxygen therapy induces vasoconstriction in the immature retina and areas of vascular occlusion may result if oxygenation is maintained.<sup>(46)</sup>

However, Jorge et al.<sup>(24)</sup> and Malheiro et al.<sup>(34)</sup> did not include oxygen therapy in their investigations of risk factors for ROP development, nor did Freitas<sup>(28)</sup> or Pereira et al.<sup>(31)</sup> Lack of sufficient data on oxygen concentrations employed and duration of oxygen therapy in medical records may explain why oxygen therapy was not a statistically significant factor in this analysis.

Several studies describe ROP as a multifactorial condition.<sup>(42)</sup> Therefore, maternal factors, fluctuating oxygen levels in the first weeks of life, mechanical ventilation, intracranial hemorrhage, blood transfusions, sepsis, congenital infections, patent ductus arteriosus, Apgar score lower than 7 at five minutes, short stature for GA and prematurity and low birth weight in particular may be implicated in ROP etiology. Twin pregnancy, intraventricular hemorrhage, phototherapy, apnea and anemia are other potential etiological factors.<sup>(47,48)</sup>

Anemia and erythropoietin administration may also be risk factors for ROP. Anemia of prematurity tends to be associated with low reticulocyte counts and defective

erythropoietin production. Given anemic states may lower oxygen saturation to a critical level, preterm newborns often require blood transfusions. The role of blood transfusions in ROP development in newborns weighing less than 1250 g at birth has been addressed in several studies and the use of recombinant human erythropoietin in an effort to lessen the need of blood transfusions in preterm newborns has been suggested. However, cumulative recombinant erythropoietin exposure (total 6-week dose) has recently been associated with an increased risk of ROP in preterm neonates.<sup>(5)</sup>

Gender and race/color are other potential newborn-related risk factors for ROP. In this study 52.9% of the NBs were males, approximately 72.7% were white, 12% were brown and were 2.7% black. However, data regarding the relationship between race/color and ROP development are conflicting. According to Sola et al.,<sup>(49)</sup> male gender and white skin color account for two out of four major risk factors for ROP. Delpont et al.<sup>(50)</sup> reported that the incidence of ROP appears to be slightly lower in black neonates relative to white neonates (3.2% and 7.4%, respectively). In turn, in the study by Fortes Filho et al.,<sup>(5)</sup> female gender was implicated.

On the maternal side, hypertensive disorders of pregnancy (HDP), diabetes mellitus and medication may play a role in ROP. Advanced maternal age and smoking are risk factors for preterm birth and low BW, respectively. Hypertensive disorders of pregnancy are often associated with perinatal morbidities and higher levels of anti-angiogenic factors such as sFlt-1 (soluble fms-like tyrosine kinase-1), a VEGF antagonist. As to diabetes, direct (e.g., increased retinal VEGF levels in response to hyperglycemia) and indirect (e.g., associations with respiratory distress syndrome) impacts on ROP development have been reported.<sup>(51)</sup>

Importantly, risk factors differed between univariate and multivariate analysis in some studies. In the study by Silva et al.,<sup>(26)</sup> different from GA and duration of oxygen therapy, birth weight, Apgar score at 1 and 5 minutes, need of surfactant and jaundice (time of onset and indirect bilirubin level) were not independent risk factors for ROP development in multivariate logistic regression analysis. However, the latter variables were significant risk factors in univariate analysis. Also, in one study<sup>(29)</sup> caffeine was a protective factor against ROP, whereas another study<sup>(31)</sup> described resuscitation in the delivery room as being protective.

Unlike other selected articles, Rover et al.<sup>(15)</sup> examined the consequences of ROP and described relationships between growth deficit in the first and second trimesters of life and very low BW, since BW interferes with weight gain

and height in preterm newborns. In NBs up to 3 months of age, ROP increases the risk of failure to thrive and is associated with a 7.2-fold higher risk of weight deficit and a 15-fold higher risk of height deficit.

Retinopathy of prematurity is a multifactorial disease associated primarily with low BW and oxygen therapy. Findings of this study and existing incidence data suggest that, in spite of the avoidable and reversible nature of ROP, risk factors for this condition deserve further investigation in order to mitigate long-term consequences. The significance of early diagnosis and appropriate treatment in the initial phase of the disease in order to prevent progression to visual impairment or blindness in preterm newborns has been emphasized.

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