

Incidence and Risk Factors of Retinopathy of Prematurity in a Spanish Tertiary Hospital

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Abstract

Background: Retinopathy of prematurity (ROP) is a vasculoproliferative retinal disorder that affects mainly preterm infants. It is one of the main causes of blindness in infants being the cause of 15% of the blindness in children in developed countries. The purpose of the present study is to determine the incidence and risk factors of ROP in a Spanish tertiary hospital.

Methods: A retrospective cohort study of newborn infants with ≤ 1500 g birth weight (BW) was conducted from January 2014 to June 2019. ROP exam results and risk factors were recorded. Descriptive and correlational statistics were performed.

Results: 223 neonates were evaluated. Mean BW \pm standard deviation (SD) was 1144.89 ± 262.46 g and mean gestational age (GA) \pm SD was 29.2 ± 3.2 weeks. The incidence of any stage of ROP was 11.2% and 3.1% of the screened newborns required treatment. All the infants treated were ≤ 28 weeks GA. The incidences of ROP in the newborns with ≤ 28 weeks GA, BW ≤ 750 g and BW 751 - 1000g were 27.4%, 45.5% and 24.4% respectively and, only 3.3% of the patients with GA > 28 weeks and 2.6% of those with BW > 1000 g developed ROP. The main risk factors were GA, BW, oxygen-therapy, invasive mechanical ventilation use, sepsis, transfusion, length of stay and absence of multiple pregnancy but the logistic regression analysis only indicated the BW as independent risk factor with an odds ratio of 8.4 in newborns weighing ≤ 750 g and an odds ratio of 5.4 in newborns weighing 751 - 1000g.

Conclusion: The results show that the incidence of ROP in our region is relatively low. However, the incidence is high in newborns with GA ≤ 28 weeks and BW ≤ 1000 g and the screening should be specially careful in those cases. The BW was the only independent risk factor for developing ROP in our hospital.

Keywords: Retinopathy of Prematurity; Birth Weight; Gestational Age; Risk Factors; Incidence

Abbreviations

ROP: Retinopathy of Prematurity; BW: Birth Weight; SD: Standard Deviation; GA: Gestational Age; WHO: World Health Organization; HUD: Donostia University Hospital; EMR: Electronic Medical Records; IUGR: Intrauterine Growth Restriction; NEC: Necrotizing Enterocolitis; LOS: Length of Stay; DB: Database; SC: Single Centre; MC: Multicentre; SPC: Subjective Paediatric Criteria; O₂: Oxygen

Introduction

Retinopathy of prematurity (ROP) is a vasculoproliferative retinal disorder that affects mainly preterm infants [1]. It is one of the main causes of blindness in infants and affects about 50,000 children worldwide [2] being the cause of 15 % of the blindness in children in developed countries [3,4].

Terry first described ROP in 1942 [5]. Since then, incidence has changed because of the differences in the use of oxygen-therapy in the newborn and the survival rate in preterm newborn, among other variables [6]. In 1968, the World Health Organization (WHO) published the first guide for the screening of ROP [7] which was applied in Spain in the 90's [8].

Even if there are many studies reporting risk factors for ROP, individually the results differ between studies.

Aim of the Study

The aim of this study is to determine the ROP incidence in our population between January 2014 and June 2019 and to compare the results to other developed countries as well as to determine the risk factors of ROP in premature infants in Gipuzkoa, North of Spain.

Materials and Methods

This is a retrospective observational study of newborn infants screened between the first of January 2014 and the 30th of June 2019 at the Donostia University Hospital (HUD). The screening was performed in newborns whose birth weight (BW) was less than or equal to 1500g of any gestational age (GA). Newborns that missed the initial examination due to death or change of hospital were excluded. The data was obtained from the Neosoft database and Microsoft Office Excel 2007 (Version 15.32) was used as the database for the study. Likewise, the clinical data was completed according to the electronic medical records (EMR) using the Osabide Global program.

The variables of interest were GA, BW, gender, delivery, eclampsia/pre-eclampsia, chorioamnionitis, multiple pregnancy, assisted reproduction, intrauterine growth restriction (IUGR), oxygen-therapy, transfusions, length of stay, sepsis, intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis (NEC) and the need for mechanical ventilation.

Two specialist ophthalmologists carried out the ophthalmological examination after pharmacological pupil dilation using a binocular indirect ophthalmoscope and a 28-diopter spherical lens.

The ROP classification was made according to the latest updates from the international classification of retinopathy of prematurity (ICROP) [9]. In this study, mild ROP was defined as ROP stages 1 - 2 and severe ROP was defined as stages 3 - 5 or presence of plus disease. The criteria for treatment were: aggressive posterior ROP and type 1 ROP (zone I any stage ROP with plus disease, zone I stage 3 without plus and zone 2 stage 2 or 3 with plus disease) [10].

Data were analyzed using IBM SPSS Statistics 25.0. Results are presented in numbers (n), frequencies (%) and means with their respective standard deviations (SD). In the univariate analysis, Chi-Square was used to analyze categorical variables and t-Student for continuous variables. Statistical significance was accepted as a p value < 0.05. Risk factors found to be significant in the univariate analysis were included in the logistic regression model. In the logistic regression model no-ROP versus ROP were compared. Odds ratios and 95% confidence intervals for each risk factor were determined.

Results

During the study period 20,601 births were registered in the HUD and 235 fulfilled the screening criteria. Twelve patients were excluded due to death or lack of follow-up. Therefore, a total of 223 newborn were included in this study, 114 girls (51.1%) and 109 (48.9%) boys. The mean GA in the screened population was 29.2 ± 3.2 weeks and the mean BW 1144.9 ± 262.5 g. The mean BW in patients with confirmed ROP was 744.3g. The incidence of ROP in the screened population was 11.2% (25 cases of ROP) and it was classified as severe (ROP stages 3 - 5 or plus) in 3.5% (n = 8) of the cases and non-severe (ROP stages 1 - 2) in 7.1% (n = 16) of the cases. No infants in our study progressed to stage 4 or 5 ROP. One case of ROP was not classified because of missing data.

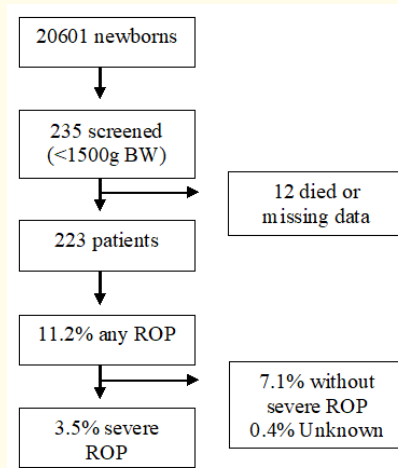


Figure 1: Flow chart of the patients and results of the study.
ROP: Retinopathy of Prematurity; BW: Birth Weight.

The 3.1% (n = 7) of the patients required treatment in our centre; 5 cases were treated with laser-therapy and 2 cases with intravitreal anti-VEGF injection. No child required surgery. One patient died before being treated. All the infants treated were ≤ 28 weeks GA.

The 45.5% of the newborns with BW ≤ 750 g and the 24.4% with BW 751-100g developed ROP, as well as, the 27.4% of the patients with ≤ 28 weeks GA. Table 1 shows the incidence according to gestational age and birth weight in our cohort.

Univariate analysis was performed to determine the association between ROP and possible risk factors. Univariate analysis indicates statistically significant differences in terms of lower BW ($p < 0.001$) and lower GA ($p < 0.001$) in newborns with ROP. Likewise, it shows a greater need for invasive mechanical ventilation ($p < 0.001$), oxygen-therapy ($p = 0.007$) and transfusions ($p < 0.001$) and a greater length of stay ($p < 0.001$) in patients with ROP. Furthermore, ROP is more frequently associated with sepsis ($p = 0.01$) and the newborns with ROP are less likely the product of multiple pregnancy ($p = 0.047$). Table 2 shows the results of the univariate analysis.

	Infant with ROP N (%)	Infant without ROP N (%)	Total
GA (weeks)			
≤ 28	20 (27.4)	53 (72.6)	73
> 28	5 (3.3)	145 (96.7)	150
BW (g)			
≤ 750	10 (45.5)	12 (54.5)	22
751 - 1000	11 (24.4)	34 (75.6)	45
> 1000	4 (2.6)	152 (97.4)	156

Table 1: Retinopathy of prematurity (ROP) in our cohort in relation to gestational age (GA) and birth weight (BW).

Variable		ROP (N:25) %	No ROP (N:198) %	p value
Female (N, %)		16 (64)	98 (49.5)	0.17
BW (N, %)	≤ 750	10 (40)	12 (6.1)	< 0.001
	751 - 1000	11 (44)	34 (17.2)	
	> 1000	4 (16)	152 (76.8)	
GA (Mean ± SD)		26.6 ± 1.9	29.5 ± 3.2	< 0.001
Assisted conception (N, %)		7 (28)	72 (36.5)	0.4
IUGR (N, %)		2 (8)	31 (15.7)	0.31
Multiple pregnancy (N, %)		7 (28)	97 (49)	0.047
Mechanical ventilation (N, %)	Invasive	18 (72)	62 (31.3)	< 0.001
	Non-Invasive	6 (24)	111 (56.1)	
	None	1 (4)	25 (12.6)	
Sepsis (N, %)		17 (68)	68 (34.3)	0.01
Intraventricular hemorrhage (N, %)		11 (44)	55 (27.8)	0.94
Bronchopulmonary dysplasia (N, %)		25 (100)	163 (82.7)	0.024
Necrotizing enterocolitis (N, %)		3 (12)	8 (4)	0.84
Delivery (N, %)	Eutocic	8 (32)	49 (24.7)	0.575
	Cesarea	16 (64)	145 (73.2)	
	Instrumented	1 (4)	4 (2)	
Eclampsia/Pre-eclampsia (N, %)	Eclampsia	0 (0)	4 (2)	0.445
	Pre-eclampsia	1 (4)	24 (12.4)	
	None	24 (96)	173 (87.3)	
Chorioamnionitis (N, %)		5 (20)	25 (12)	0.309
Oxygen-therapy (N, %)		24 (96)	140 (70.7)	0.007
Transfusions (N, %)		17 (68)	50 (25.3)	<0.001
Length of stay (Mean ± SD)		96 ± 41	54.6 ± 24.7	<0.001

Table 2: Clinical and demographic characteristics of newborns with retinopathy of prematurity (ROP) vs without retinopathy of prematurity (No ROP). The p values were calculated using the t-Student for continuous variables and Chi-square for categorical variables.

BW: Birth Weight (g); GA: Gestational Age (weeks); IUGR: Intrauterine Growth Restriction.

Logistic regression analysis was performed to evaluate independent risk factors. Birth weight was an independent risk factor with OR 8.4 in newborns weighing ≤ 750g and OR 5.4 in newborns weighing 751 - 1000g. No other variable showed statistical significance. Table 3 shows the results of the logistic regression.

Risk Factor	Odds Ratio and (95% confidence interval)	p value
Birth Weight ≤ 750g *	8.391 (1.576 - 44.66)	0.013
Birth Weight 751 - 1000g *	5.362 (1.346 - 21.350)	0.017
Length of stay (days)	1.015 (0.996 - 1.035)	0.115
Multiple pregnancy	0.414 (0.141 - 1.216)	0.109
Sepsis	0.865 (0.264 - 2.835)	0.811
Transfusions	1.240 (0.375 - 4.103)	0.725
Gestational age (days)	0.975 (0.943 - 1.008)	0.138
Oxygen-therapy	2.338 (0.249 - 21.918)	0.457
Mechanical ventilation	∓	∓
Bronchopulmonary dysplasia	∓	∓

Table 3: Odds ratios of the multivariate logistic regression analysis of risk factors in patients with ROP.

*: Odds ratios for birth weight ≤ 700g and 751 - 1000g are compared to reference category birth weight > 1000g.

∓: Variable entered in the model but excluded from the final regression equation.

Discussion

In the present study the incidence of any stage ROP in the newborns weighing ≤ 1500g was 11.2% and only 3.1% of the screened newborns required treatment. The results of some other recent studies regarding incidence of any stage ROP and ROP needing treatment are shown in the table 4.

First Author	Country	Patients (years)	Study type	Screening criteria	Incidence of any stage ROP (%)	Treated ROP (%)
North America						
Ludwig CA. [11]	USA	153,706 (2006, 2009,2012)	Retrospective cross sectional MC	>28 LOS	17.9	8.3
Port AD [12]	USA	1354 (2002-2010)	Retrospective cohort MC	BW ≤1500 or GA <30 or SPC	38.8	5.9
Quinn GE [13]	USA and Canada	7483 (2006-2011)	Retrospective cohort MC	BW ≤ 1500 or GA ≤ 30	43.1	6.9
Mitsiakos G [14]	Canada	1562 (1994-2008)	Retrospective cohort SC	GA < 32	15.6	5.2
Isaza G [15]	Canada	623 (2010-2016)	Retrospective cohort SC	BW < 1500 or GA < 32	67.1	7
Europe						
Holmström G [16]	Sweden	1784 (2008-2009)	Retrospective cohort DB	<32 GA	24.1	4.4
Mataftsi A [17]	Greece	1178 (2004-2015)	Retrospective cohort SC	BW ≤ 1500 or GA ≤ 32	19.7	2.5

Larsen PP [18]	Germany	863 (2012-2016)	Retrospective cohort SC	BW ≤ 1500 or GA ≤ 32 or GA ≤ 36 with O ₂ -therapy > 3 days	27.5	2.5
Holmstrom G [19]	Sweden	7249 (2008-2017)	Retrospective cohort DB	GA < 31	31.9	6.1
Chan H [20]	France	419 (2009-2015)	Retrospective cohort SC	BW < 1500 or GA < 32 or GA 1500-2000 with SPC	27.7	6.6
Gerull R [21]	Switzerland	6472 (2006-2015)	Retrospective cohort DB	BW < 1500 or GA < 31-32	9.3	1.2
Spain						
Present study, Basasoro A.	Spain	2014-2019	Retrospective cohort SC	BW ≤ 1500	11.2	3.1
Hernandez M [22]	Spain	115 (2004)	Retrospective cohort MC	BW ≤ 1500 or GA ≤ 32	32.1	15.6
Montañez FJ [23]	Spain	446 (1992-2003)	Retrospective cohort	BW ≤ 1500 or assisted O ₂ -therapy	33.2	12.3
Grunauer N [24]	Spain	324 (1996-2001)		GA ≤ 32	21.7	3.1
Rodriguez-Hurtado FJ [25]	Spain	303 (1995-2003)	Retrospective cohort SC	BW ≤ 1500 GA < 32 or SPC	13.2	3
Asia						
Sarikabadayi YU [26]	Turkey	700 (2009)	Prospective cohort SC	<34 GA or BW < 2000	32.7	3.1
Bas AY [27]	Turkey	6115 (2016-2017)	Prospective cohort MC	BW ≤ 1500 or GA ≤ 32 or SPC	27	6.7
Vasavada D [28]	India	280 (2012-2013)	Prospective cohort MC	BW < 1700 or GA < 34	19.3	10.3
Xu Y [29]	China	2825 (2010-2012)	Prospective cohort SC	BW ≤ 2000 or GA ≤ 34	17.8	6.8
Leng Y [30]	China	436 (2013-2017)	Prospective cohort SC	BW < 2000 or GA < 32	31.7	14
Chow PPC [31]	Hong Kong	754 (2007-2015)	Retrospective cohort SC	BW < 1500 or GA < 32	31	4.5
Luk AS [32]	Hong Kong	602 (2008-2015)	Retrospective cohort SC	BW ≤ 1500 or GA < 32	28.2	3.8
Kang EY [33]	Taiwan	11180 (2002-2011)	Retrospective cross-sectional	LOS > 28	36.6	6.5
Central and South America						
Alda E [34]	Argentina	3695 (2004 and 2016)	Retrospective cohort (DB)	BW < 1500 or GA ≤ 32	22.7	7.8

Garcia H [35]	Mexico	326 (2009-2013)	Retrospective cohort SC	BW ≤ 1500 or GA ≤ 32	47.8	34
Freitas AM [36]	Brasil	602 (2005-2015)	Retrospective cohort SC	BW ≤ 1500 or GA ≤ 32 or SPC	33.9	5
Tabarez-Carvajal AC [37]	Costa Rica	3018 (2010-2014)	Retrospective cohort DB	BW ≤ 1750 or GA ≤ 34	19.4	15.4
Africa						
Onyango O [38]	Kenia	103 (2010-2015)	Retrospective cohort SC	BW ≤ 1500 or GA ≤ 32	41.7	8.7

Table 4: Previous studies of retinopathy of prematurity (ROP) incidence.

BW: Birth Weight (g); GA: Gestational Age (Weeks); LOS: Length of Stay (Days); DB: Database; SC: Single Centre; MC: Multicentre; SPC: Subjective Paediatric Criteria; Oxygen: O₂

It is obvious that the screening and treatment criteria used in the different studies differ and it leads to difficulties to directly compare the results obtained. Furthermore, the availability of life-preserving technologies and the locally defined limit to viability in newborns are not the same in-between countries which is an obstacle in order to create an unified screening criteria. The incidence of any type of ROP goes from 9.3% [21] to 67.1% [15] in the revised studies shown in table 4 and it could be due to inter-observer variability which may carry under-diagnosis that specially happens in the mild cases. The incidence of treatment requiring ROP goes from 1.2% [17] to 34% [34] but further analysis of the studies with the highest incidences shows some limitations of these studies. Garcia., *et al.* [35] refers 54 out of 156 cases of mild ROP treated and Hernandez., *et al.* [22] includes 5 patients treated with pre-threshold stage ROP. Equally, Rodriguez-Hurtado FJ [25] referred a low incidence of any type of ROP and treated ROP and they suggested that the inclusion criteria for 28% of the screened population was subjective paediatric criteria and this could be the reason of having such a low incidence. Anyway, it seems that the incidence of any stage of ROP and the ROP needing treatment are greater in North America than in Europe and it could be interesting to analyze it in further studies. Our results go along with other recent studies shown in the table, for example, Ludwig., *et al.* [11] found a ROP incidence of 30.2% in the infants between 751 - 1000g which is comparable to our study (24.4%).

To our knowledge, there have not been published recent studies undergone in our country and the changes in treatment criteria and screening criteria hampers the direct comparison of the results with other Spanish centres.

The American Academy of Ophthalmology’s ROP screening guidelines recommend the screening in all infants with BW ≤ 1500g, GA ≤ 30 weeks and those who have a BW 1500-2000g or a GA > 30 weeks who are believed by their attending paediatrician or neonatologist to be at risk for ROP [39]. In that way, there have been several attempts in order to create new screening models. Recently, a Swedish study [40] has published the results of a new screening model in infants with GA 24 - 28 weeks called DIGIROP with 15.1% less examinations than the US model. Surprisingly, the mean BW and the mean GA of the population in the Swedish study are comparable to our study (28.1 weeks GA and 1119g BW in Sweden and 29.1 weeks GA and 1144g BW in our study) even if they get higher incidence and treatment rates (31.9% and 5.8% respectively). In the Basque Country there is a low birth rate, the birth-rate per 1,000 population in Gipuzkoa was 7.6% in 2018 [41] and there was an average of 49.5 premature children screened per year. Because of this, the aim of our screening is to avoid missing any positive cases (aim for high sensitivity) rather than having less examinations, in consequence we do not consider that our population would benefit of the Swedish model for the screening of ROP.

In our hospital the screening criteria is $BW \leq 1500g$ of any gestational age and the literature shows that there are cases of ROP in infants with $BW > 1500g$. As an example, the study realized by Alexander, *et al.* (Port., *et al.* 1669 - 1677) found that 13.5% of the cases of ROP (183 of 1354 cases) were detected in newborns with $BW > 1500g$ but none of these infants needed treatment. In that way, there were no cases of patients requiring treatment with a $GA > 28$ weeks in our study and it goes along with the study published by Gerull, *et al.* [21] which declares that newborns $GA < 28$ weeks are more frequently treated. Nevertheless, the same study exposes a ROP case in a patient with $GA 30+1$ and $BW 1530g$ that required treatment. Those results in addition to the low birth-rate in our area suggest that we should include the GA in the screening criteria in our centre even if probably most of them would be mild cases not needing treatment.

In the present study, the incidences of ROP in the newborns with ≤ 28 weeks GA , $BW \leq 750g$ and $BW 751 - 1000g$ were 27.4%, 45.5% and 24.4% respectively. On the other hand, only the 3.3% of the patients with $GA > 28$ weeks and the 2.6% of those with $BW > 1000g$ developed ROP. Thus, the results under light the importance of taking special care when screening newborns with ≤ 28 weeks GA or $BW \leq 1000g$.

Many risk factors have been reported in the literature that predispose ROP. In this study univariate analysis showed significant relation between GA , BW , oxygen-therapy, use of invasive mechanical ventilation, sepsis, transfusion, bronchopulmonary dysplasia, length of stay and absence of multiple pregnancy. Gender, delivery, assisted reproduction, eclampsia/pre-eclampsia, chorioamnionitis, IUGR, intraventricular hemorrhage and NEC were not associated with severe ROP. All the risk factors have been previously associated to ROP in the literature [11,12,26].

The multivariate regression analysis shows that the only independent risk factor in our study was the BW . We have found that newborns with $\leq 750g$ and $751 - 1000g$ BW had a higher risk of developing ROP (OR 8.4 and OR 5.4 respectively). The current literature under lights the importance of the GA and the BW as the crucial risk factors to determine the risk to develop ROP. The population analyzed in our study may not be big enough to determine if some other risk factors could be independent as well and further research with more patients would be needed for confirming our results.

Likewise, having access to retinography (for example Retcam®) could be extremely useful in order to document the cases objectively and to compare the present study with other international studies as well as its potential use as teaching material. In addition, an objective evaluation could be helpful to avoid the inter-observer variability in diagnosis and limit its influence in the incidence differences between centres. Unfortunately, we do not have it available in our centre.

Being this a retrospective study it is not extent of limitations. The sample size was limited, indeed the low birth-rate in our zone allows a small recruitment even if the study period gets almost 5 years, and probably a multicentre study would be an option to improve that limitation. In addition, the follow-up of this study was not long because the analyzed population was born this decade. The number of clinical and demographical risk factors included in this study were limited. However, the risk factors chosen for the analysis were cited in the literature.

Conclusion

In conclusion, the present study shows that the incidence of ROP in our region is lower than previous reports in Spain and Europe. The main risk factors are GA , BW , oxygen-therapy, invasive mechanical ventilation use, sepsis, transfusion, length of stay and absence of multiple pregnancy but the logistic regression analysis only indicates the BW as independent risk factor. Because of the low birth-rate in

our region we consider that screening should be made not only in newborns with BW \leq 1500g but also in those with GA \leq 30 weeks. The ROP incidence is high in newborns with GA \leq 28 weeks and BW \leq 1000g and the screening must be especially careful in those cases. A larger study with longer period of follow-up is necessary to better define the risk factors in our population.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Ethical Approval

The study was approved by the hospital's Ethics Committee. All research adhered to the declaration of Helsinki.

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