Incidence and risk factors for retinopathy of prematurity in the West Black Sea region, Turkey

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The objective of this study was to determine the incidence, risk factors and severity of retinopathy of prematurity (ROP) and to establish screening criteria for our region. Data on 330 infants with gestational age at birth ≤34 weeks were analyzed retrospectively for a ROP diagnosis and risk factors. Infants with type 1 ROP were treated with argon laser photocoagulation. ROP was detected in 106 of 330 infants; 18 infants had type 1 ROP and were treated. Two infants with ROP that progressed to stage 4 disease required surgery. No treatment was needed in infants born after 32 weeks of gestation. Respiratory distress syndrome and low gestational age were the most important risk factors for type 1 ROP. In the West Black Sea region of Turkey, screening all premature infants with a gestational age ≤32 weeks or a birth weight ≤1900 g appears to be appropriate.

Key words: in vitro fertilization, respiratory distress syndrome, retinopathy of prematurity.

Retinopathy of prematurity (ROP) is a major treatable cause of blindness worldwide. The rate of blindness varies considerably in different care units, depending on their level of development and whether effective screening and treatment programs exist[1]. Numerous conditions or stimuli can contribute to the risk of developing ROP, and many studies have investigated these. The major parameters are reportedly low birth weight (BW) and low gestational age (GA)[2]. Other risks include respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), sepsis, blood transfusion, apnea, prolonged parenteral nutrition, and duration of artificial ventilation[1].

In this study, the incidence, possible risk factors and the results of treatment for ROP were examined in a tertiary neonatal intensive care unit (NICU) in Zonguldak, Turkey.

Material and Methods

This study was a retrospective review of the medical records of premature infants who were examined for ROP and were born between September 2005 and July 2009. In total, 330 premature infants with GA at birth ≤34 weeks were examined by a single ophthalmologist for ROP screening at the NICU of Zonguldak Karaelmas University, Turkey. Infants were included in this study if they were born in our hospital or if they were transferred from surrounding hospitals to our hospital for an initial ROP examination. Infants with ocular anomalies such as congenital cataracts, microphthalmia, anophthalmia, or coloboma in one or both eyes or systemic anomalies, or those who *died* during the follow-up period or were unavailable for follow-up were excluded from the study. The initial examination was performed on infants at 31 weeks of postconceptional age if the infants were <28 weeks GA or 4 weeks after birth, whichever was earlier[3]. Pupils were dilated using 2.5% phenylephrine and 0.5% tropicamide, instilled twice at an interval of 10 minutes (min). The fundus was examined with a binocular indirect ophthalmoscope and +20 D lens, lid speculum, and scleral depressor approximately 45 min after the first instillation. A drop of 0.5% proparacaine was used for topical anesthesia. ROP findings were classified according to the International Classification of ROP[4]. Follow-up examinations were performed

at 1–3-week intervals, depending on the findings of each examination. Infants with normal vascularization of the retina to the periphery were not re-examined. Infants were treated with indirect ophthalmoscopic argon laser photocoagulation [OcuLight GL (532 nm) Laser Photo-coagulator] of the entire avascular retina with near confluent burns when type 1 ROP developed, as determined by the Early Treatment for Retinopathy of Prematurity (ETROP) study[5]. Laser parameters were approximately 300 mW power and 200–300 ms exposure time. All laser treatments were conducted under topical anesthesia (a drop of 0.5% proparacaine hydrochloride solution instilled) and intravenous sedation (ketamine 1 mg/kg) with a neonatologist on standby. Topical treatment of 1 drop of dexamethasone-tobramycin 0.05%–0.3% ophthalmic suspension was administered in the eyes 3 times daily for 5 days, for prophylaxis of bacterial conjunctivitis and inflammation. Follow-up examinations were performed at 7-day (or less) intervals until ROP regressed or until additional treatment was deemed necessary. Additional treatment was performed in the event of skipped areas.

Premature infants' gender, BW, GA at birth, multiple births, *in vitro* fertilization (IVF), RDS, intrauterine growth retardation (IUGR), apnea [breathing pauses lasting for >20 seconds (s) or for >10 s if associated with bradycardia[6]], oxygen therapy (≥ 28 days), anemia, and blood transfusions were analyzed by logistic regression.

Statistical Analysis

Statistical analyses were performed using SPSS software (ver. 13.0). Qualitative variables, such as the presence or absence of a neonatal risk factor, were evaluated using the chi-squared test. Quantitative data, such as GA and BW, were tested using Student's *t*-test or ANOVA. Statistical significance was defined as $p<0.05$. Stepwise multivariate logistic regression was used to evaluate factors predictive of developing ROP. The odds ratio and 95% confidence interval for each possible risk factor were also calculated.

Results

Of the 330 infants (mean GA: 31±2.4 weeks, mean BW: 1589.5±438 g), 173 were male and 157 were female. Of these, 132 (40.0%) were multiple births: 112 twins, 19 triplets, and 1 quadruplet. Twenty-one infants were conceived by IVF, of whom 18 (85.7%) were from multiple pregnancies: 7 (33.3%) twins, 10 (47.6%) triplets, and 1 quadruplet. ROP was detected in 106 (32.1%) infants, and of these, 16 were from IVF pregnancies. Eighteen (5.4%) infants were diagnosed with type 1 ROP and treated with binocular indirect argon laser photocoagulation to the avascular retina.

Eleven risk factors were investigated. GA, BW, apnea, RDS, prolonged oxygen therapy, anemia, blood transfusion, and IVF were significant risk factors for the development of ROP. Other parameters, including gender, IUGR and number of births, were not found to be significant factors for the development of ROP in our study (Table I). Those factors that were statistically significant were analyzed using a forward stepwise logistic regression analysis. BW, RDS and IVF remained significant independent risk factors for ROP (Table II). GA and RDS were found to be the most important risk factors for the development of type 1 ROP in the forward stepwise logistic regression analysis (Table III).

Signs of ROP regression after laser therapy were not observed in five eyes of three infants and required additional laser therapy for skipped areas. Three of those eyes in two infants progressed to stage 4a ROP and were referred to another center for vitreoretinal surgery. In other laser-treated eyes, signs of ROP and disease regression were observed during the first week, and these were almost completely resolved at 4 weeks after the laser therapy.

The mean GA and BW for infants with type 1 ROP were calculated as 27.6±1.8 weeks and 1025±332 g, compared with 29.7±2.2 weeks and 1399.8±388 g for those not reaching the type 1 ROP.

Retinopathy of prematurity (ROP) was present in 43.2% of the infants with GA ≤32 weeks and 9.3% of the infants with GA >32 weeks. On the other hand, type 1 ROP was present in 8.1% of the infants with GA ≤32 weeks and in no infant with GA >32 weeks. ROP was diagnosed in 50% of infants with BW ≤1500 g and 18.6% of infants with BW >1500 g. Type 1 ROP was diagnosed in 11.3% of infants with BW ≤1500 g and in 1.1% (2) of infants

Table I. Infant Characteristics and Relationship Between Retinopathy of Prematurity and Risk Factors

Patient characteristics	All infants (n = 330)	All infants with ROP n=106 (32.1%)	All infants with Type 1 ROP n=18 (5.4%)	Surgery n=2 (0.6%)	p value
Gender Male n (%)	173 (52.5)	54 (50.9)	10 (55.6)	0	0.540
Female n (%)	157 (47.5)	52 (49.0)	8 (44.4)	2	
Gestational age (wks) (mean ± SD)	31±2.4	29.3±2.2	27.6±1.8	27.5±0.7	<0.001
Weight at birth (g) (mean ± SD)	1589.5±438	1336±403	1025±332	936±38	<0.001
Apnea n (%)	37 (22.2)	22 (20.7)	9 (50.0)	2	<0.001
RDS n (%)	115 (34.8)	62 (58.4)	16 (88.8)	2	<0.001
IUGR n (%)	37 (11.21)	15 (14.1)	7 (38.8)	1	0.244
IVF n (%)	21 (6.36)	16 (15.0)	4 (22.2)	1	<0.001
Anemia n (%)	81 (24.5)	42 (39.6)	14 (77.7)	1	<0.001
Blood transfusions n (%)	111 (33.6)	58 (54.7)	14 (77/7)	1	<0.001
Oxygen n (%)	304 (92.1)	104 (98)	18 (100)	2	0.005
Multiple births n (%)	132 (40)	45 (42.4)	6 (33.3)	0	0.462

ROP: Retinopathy of prematurity. SD: Standard deviation. RDS: Respiratory distress syndrome. IUGR: Intrauterine growth retardation. IVF: In vitro fertilization.

P value compares infants with any ROP to those without any ROP.

with BW >1500 g. One of these two infants had a GA of 30 weeks and BW of 1634 g, and additional risk factors included RDS, oxygen therapy and IVF. The other infant had GA of 32 weeks and BW of 1900 g, and additional risk factors included RDS, apnea, oxygen therapy, anemia, and blood transfusions. The GA and BW distributions for all infants are shown in Table IV.

Discussion

In this study, we found that the frequency of ROP was 32.1% in infants with GA ≤34 weeks. Two previous studies from Turkey reported ROP incidence of 55.6% and 37% in patients with GA ≤34 weeks[1,7]. Reports on the incidence of ROP within the past decade are controversial. The incidence and severity of ROP vary considerably in different care units, depending on their level of development, different populations, regions, and races[8]. It has been reported that the mean BW of infants with severe ROP is 750 g in industrialized countries and 1500 g in developing countries[9]. Chiang et al.[10] analyzed records of 15,691 infants from New York and found that the incidence of ROP was 27.3% among infants with BW <1200 g and 33.2% for infants with BW <1000 g, and the prevalence of ROP with threshold disease was 9.5%. In our study, the incidence of ROP was found to be 69.2% in infants with BW <1200 g and 75.6% in infants with BW <1000 g. In most developed countries, infants whose GA is >32 weeks or BW >1500 g are not screened. The American and British screening criteria for ROP state that infants ≤1500 g BW or ≤30 weeks GA and infants ≤1500 g BW or ≤32 weeks GA must be screened, respectively[11,12]. In this study, the frequency of ROP was 43.2% and 9.3% in infants with a GA ≤32 weeks and GA >32 weeks, and 50% and 18.6 % in infants with a BW ≤1500 g and BW >1500 g, respectively. If we use a BW criterion of ≤1500 g as the only criterion for screening, two infants >1500 g (1634 g and 1900 g) born at 30 and 32 weeks GA

Table II. Independent Risk Factors for Retinopathy of Prematurity after Logistic Regression Analysis

Variable	Odds ratio	95% confidence interval	p value
Gestational age (wks)	0.649	0.572-0.736	<0.001
Respiratory distress syndrome	3.930	2.229-6.930	<0.001
In vitro fertilization	9.247	2.833-30.187	<0.001

Table III. Independent Risk Factors for Type 1 Retinopathy of Prematurity after Logistic Regression Analysis

Variable	Odds ratio	95% confidence interval	p value
Gestational age (wks)	0.545	0.410-0.723	<0.001
Respiratory distress syndrome	27.641	3.440-222.124	0.002

who developed type 1 ROP would be missed. No infant with GA >32 weeks had type 1 ROP, consistent with the reports of Akkoyun et al.[1] and Mutlu et al.[7] Another study from Turkey reported that the frequencies of ROP were 50.9% and 23.4% in infants with a GA of <32 weeks and of 32-34 weeks, respectively, and 11 patients with GA >32 weeks required cryo/laser therapy for severe ROP[13]. It seems reasonable to screen all infants with GA ≤32 weeks or with a BW ≤1900 g.

It is likely that in developing countries or some different regions of countries, more mature infants may be at risk of advancing ROP, and this requires broader screening criteria to capture infants at risk of ROP.

We found that apnea, RDS, oxygen therapy, blood transfusion, and IVF were independent risk factors for the development of ROP. Additionally, low GA and RDS were independent risk factors for the development of type 1 ROP. Many risk factors, such as GA, BW, RDS, surfactant treatment, duration of mechanical ventilation, gender, blood transfusions, hypothermia, Apgar scores, multiple gestation, total duration of supplemental oxygen, anemia, presence of patent ductus arteriosus, sepsis, and IVH, have been widely discussed in numerous studies[1,14-19].

Few studies have evaluated the relationship between the development of ROP and IVF infants. Bergh et al.[20] reported that assisted conception likely accounts for a high proportion of cases of ROP, particularly severe ROP. Watts and Adams[21] found that 41.6% of IVF infants progressed to ROP stage 3, compared with only 9.3% of naturally conceived children. Friling et al.[22] found no significant differences in the occurrence or severity of ROP between the natural conception and assisted conception groups. In our study, IVF was found to be an independent risk factor for ROP: type 1 ROP was higher in IVF infants, although it was not a significant risk factor in the stepwise logistic regression analysis (p=0.142). Of the IVF infants, 76.1% (16/21) were diagnosed with ROP, and 19.0% (4/21) progressed to type 1 ROP compared with only 29.1% and 4.5%, respectively, of naturally fertilized (NF) infants. No significant difference was found between infants conceived by IVF and NF for BW or GA (Table V).

Our findings suggest that in the West Black Sea region of Turkey, screening of all premature infants with a GA ≤32 weeks or a BW ≤1900 g appears to be appropriate. The incidence and severity of ROP varies considerably in different care units, populations and regions. Thus, criteria for ROP screening programs should be set according to local conditions. IVF may be a new independent significant risk factor for ROP. Currently, a relationship between IVF and ROP severity has been observed in a limited number of studies. Further prospective studies of a large number of IVF infants are needed to clarify the role of IVF in ROP severity.

Table IV. Gestational Age and Birth Weight Distribution of All Infants

	GA ≤32 weeks n=222	GA >32 weeks n=108	BW ≤1500 g n=142	BW >1500 g n=188
Gestational age (wks) (mean ± SD)	29.7±1.9	33.66±0.4	29.22±2.2	32.3±1
Weight at birth (g) (mean ± SD)	1434.4±396	1908.3±337	1181±229	1898.1±275
ROP n (%)	96 (43.2)	10 (9.3)	71 (50)	35 (18.6)
Type 1 ROP n (%)	18 (8.1)	0	16 (11.3)	2 (1.1)
Surgery n (%)	2 (.9)	0	2 (1.4)	0

SD: Standard deviation. ROP: Retinopathy of prematurity. GA: Gestational age.

BW: Weight at birth.

Table V. Distribution of Retinopathy of Prematurity and Type 1 ROP by Type of Pregnancy and Characteristics

Type of pregnancy	Naturally conceived babies			IVF babies			p value
	Single n=195	Multiple n=114	Total n=309	Single n=3	Multiple n=18	Total n=21	
Gestational age (wks) (mean ± SD)	30.8 ±2.5	31.4 ±2.3	31 ±2.4	26.3 ±3.2	30.6 ±1.9	30 ±2.5	0.066
Weight at birth (g) (mean ± SD)	1581.9 ±455	1633.6 ±454	1601 ±455	1020 ±440	1613 ±413	1529 ±458	0.484
ROP n (%)	58 (29.7%)	32 (28%)	90 (29.1%)	3(100%)	13 (72.2%)	16 (76.1%)	<0.001
Type 1 ROP n (%)	10 (5.1%)	4 (3.5%)	14 (4.5%)	2 (66.6%)	2 (11.1%)	4 (19%)	0.043
Surgery n (%)	2 (1%)						

IVF: In vitro fertilization. SD: Standard deviation. ROP: Retinopathy of prematurity.

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