Retinopathy of Prematurity in Infants Born before 25 Weeks Gestation in a Korean Single Neonatal Intensive Care Unit: Incidence, Natural History and Risk Factors

Mingui Kong[1], Dong Hoon Shin[1], Sang Jin Kim[1], Don Il Ham[1], Se Woong Kang[1], Yun Sil Chang[2], and Won Soon Park[2]

Departments of [1]Ophthalmology and [2]Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Address for Correspondence:
Sang Jin Kim, MD
Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82.2-3410-6775, Fax: +82.2-3410-0074
E-mail: sangjin.kim.md@gmail.com

As younger preterm infants are able to survive, more extremely preterm infants are at risk of developing retinopathy of prematurity (ROP). To investigate the incidence, progression and risk factors of ROP in extremely preterm infants in Korea, the medical records of infants born before 25 weeks gestation were retrospectively reviewed. The criteria for laser treatment agreed with type 1 ROP as defined by the Early Treatment for Retinopathy of Prematurity study. Of the 121 infants included in the analysis, 119 (98.4%) infants developed any stage ROP, including 78 infants (64.5%) with type 1 ROP. The mean postmenstrual age (PMA) at the onset of any ROP and type 1 ROP were 33.5 and 36.1 weeks, respectively. All but one infant developed type 1 ROP after 31 weeks PMA. Univariate analysis showed that duration of total parenteral nutrition and onset of any ROP (PMA) were associated with the development of type 1 ROP. In conclusion, this study shows high incidence of ROP in extremely preterm infants and suggests that, although current screening protocols are feasible for most preterm infants born before 25 weeks gestation, earlier screening before 31 weeks PMA may be necessary in infants with an unstable clinical course.

Key Words: Retinopathy of Prematurity; Infant, Premature; Infant, Low Birth Weight

INTRODUCTION

Retinopathy of prematurity (ROP), a disease that affects immature vasculature in the eyes of premature infants, remains a major cause of blindness and visual impairment in children worldwide (1, 2). Proper screening and timely treatment are essential in improving anatomical and functional outcome (3, 4). As younger preterm infants are able to survive due to the advances in neonatal intensive care, more extremely preterm infants are at risk of developing ROP (5, 6). However, the epidemiology and natural history of ROP in infants born before 25 weeks gestation have not been investigated in depth, especially in Asian countries. The current screening protocol is based on the early treatment for retinopathy of prematurity (ET-ROP) study and cryotherapy for retinopathy of prematurity (CRYO-ROP) study (7-11). These previously published studies involved only a small number of extremely preterm infants because they were conducted more than a decade ago, during which the survival rates of infants born before 25 weeks gestation were low. Therefore, the current screening protocol may not be suitable for these extremely preterm infants.

This study aimed to evaluate the incidence and progression of ROP in infants born before 25 weeks gestation in a neonatal intensive care unit in Korea. In addition, ocular and systemic risk factors for ROP that require treatment were investigated. This study analyzed 121 infants with the gestational age (GA) of 22 to 24, one of the largest cohort reported among single center studies. This study may help elucidate the natural history of ROP in extremely preterm infants and to provide the proper time of screening.

MATERIALS AND METHODS

The medical records of consecutive preterm infants born before 25 weeks gestation who were admitted to the Samsung Medical Center neonatal intensive care unit from March 2004 to November 2011 were retrospectively reviewed. Exclusion criteria were as follows: infants who died before or within the screening period, incomplete follow-up, and lack of adequate systemic information. ROP was categorized according to the revised International Classification of Retinopathy of Prematurity (IC-ROP) (12). Aggressive posterior ROP (AP-ROP) was defined as a se-

vere form of ROP characterized by its posterior location, prominence of plus disease, the ill-defined nature of the retinopathy, and the rapid progression (12). The screening examination for ROP followed the guidelines proposed by the American Academy of Ophthalmology and Pediatrics and Association for Pediatric Ophthalmology and Strabismus with some modifications (7). The first screening examination was undertaken at 29 to 31 weeks postmenstrual age (PMA). Treatment criteria were based on ET-ROP type 1 disease including zone I, any stage ROP with plus disease, zone I, stage 3 ROP with or without plus disease, and zone II, stage 2 or 3 ROP with plus disease (9, 10).

Fundus findings on ROP screening until the development of type 1 ROP or termination of screening were analyzed. If the two eyes showed asymmetry in progression and severity of ROP, data on the worse eye was included in the analysis. In addition, systemic parameters were retrieved including birth weight, Apgar score, multiple births, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), sepsis, use of surfactant, transfusion, duration of total parenteral nutrition (TPN), and duration of oxygen therapy including mechanical ventilation and continuous positive airway pressure (CPAP).

The incidence of any ROP and type 1 ROP by GA was determined by Kaplan-Meier survival analysis. Differences in time to development of any ROP and type 1 ROP between the GA groups were analyzed by the log-rank test. Univariate analysis was conducted with the Student's t-test, Mann–Whitney U-test, Fisher's exact test, or chi-square test on systemic and ocular parameters. Multiple logistic regression analysis was used to identify param-

eters significantly and independently associated with type 1 ROP. Variables with a significant correlation or a tendency towards an association with type 1 ROP in univariate analysis ($P < 0.2$) were entered into a logistic regression model. P values of < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA).

Ethics statement

The study followed the tenets of the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional review board of Samsung Medical Center (IRB No. SMC 2012-04-040). Informed consent was exempted by the board.

RESULTS

During the study period, a total of 182 infants born before 25 weeks gestation were enrolled (Fig. 1). Of these, 55 infants died before the ophthalmologic screening for ROP and additional 6 infants died before the completion of the ROP screening protocol. Finally, 121 infants born before 25 weeks gestation were included in the analysis (Fig. 1). Demographic and systemic characteristics of included infants are shown in Table 1. The mean GA of included infants was 24.0 ± 0.6 weeks (range, 22.4-24.9). The mean birth weight was 652.9 ± 109.3 g (range, 370-1,104 g).

Of the 121 infants, 119 (98.4%) infants developed ROP. Thirty-seven (30.6%) infants developed mild ROP (stages 1-2), and 82 (67.8%) infants developed severe ROP (stages 3-5). The incidences of maximum stages of ROP in relation to GA at birth are
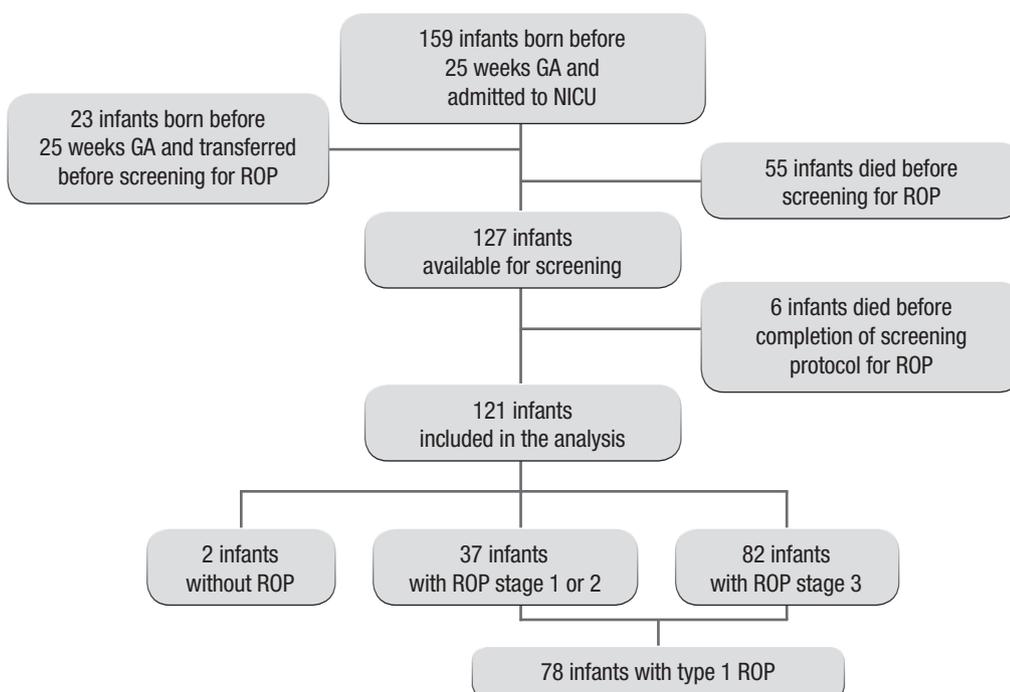

Fig. 1. Flow-chart of the study population. GA, gestational age; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity.

Table 1. Incidence, maximal stage of retinopathy of prematurity (ROP), and clinical characteristics of included infants born before 25 weeks gestation

Parameters	Gestation age			
	22 weeks (n = 5)	23 weeks (n = 42)	24 weeks (n = 74)	Total (n = 121)
Maximal stage of ROP				
No ROP	0 (0)	0 (0)	2 (2.7)	2 (1.7)
ROP	5 (100)	42 (100)	72 (97.3)	119 (98.4)
Stage 1	0 (0)	5 (11.9)	6 (8.1)	11 (9.1)
Stage 2	0 (0)	11 (26.2)	15 (20.3)	26 (21.5)
Stage 3	3 (60)	23 (54.8)	50 (67.6)	76 (62.8)
Stage 4	0 (0)	3 (7.1)	0 (0)	3 (2.5)
Stage 5	2 (40)	0 (0)	1 (1.4)	3 (2.5)
Type 1 ROP	5 (100)	28 (66.7)	45 (60.8)	78 (64.5)
AP-ROP	2 (40)	5 (11.9)	10 (13.5)	17 (14.0)
Clinical characteristics				
Gender, No. of male (%)	3 (60.0)	19 (45.2)	37 (50.0)	59 (48.8)
Birth weight (g, Mean ± SD) (range)	511.4 ± 108.7	588.3 ± 68.3	699.1 ± 102.1	652.9 ± 109.3
	(370-647)	(441-720)	(440-1,104)	(370-1,104)
VSGA No. (%)	0 (0)	0 (0)	1 (1.4)	1 (0.8)
SGA No. (%)	1 (20.0)	3 (7.1)	2 (2.7)	6 (5.0)
AGA No. (%)	4 (80.0)	39 (92.9)	71 (95.9)	114 (94.2)
Multiple births No. (%)				
Single	3 (60)	23 (54.8)	48 (64.8)	74 (61.2)
Twin	2 (40)	16 (38.1)	25 (33.8)	43 (35.5)
Triplet	0 (0)	3 (7.1)	1 (1.4)	4 (3.3)
Apgar score (Mean ± SD)				
1 min	3.3 ± 1.3	3.9 ± 1.4	4.4 ± 1.5	4.2 ± 1.5
5 min	6.3 ± 1.3	6.7 ± 1.5	6.9 ± 1.4	6.8 ± 1.4
PDA ligation No. (%)	4 (80)	36 (85.7)	46 (62.2)	86 (71.1)
IVH grade No. (%)				
None	1 (20)	3 (7.1)	30 (40.5)	34 (28.1)
Grade I	1 (20)	6 (14.3)	14 (18.9)	21 (17.4)
Grade II	0 (0)	14 (33.3)	9 (12.2)	23 (19.0)
Grade III	3 (60)	13 (30.9)	15 (20.3)	31 (25.6)
Grade IV	0 (0)	6 (14.3)	6 (8.1)	12 (9.9)
BPD ≥ moderate No. (%)	4 (80)	34 (80.9)	40 (54.1)	78 (64.4)
NEC operation No. (%)	2 (40)	9 (21.4)	9 (12.2)	20 (16.5)
Culture-proven sepsis No. (%)	5 (100)	11 (26.2)	17 (22.9)	33 (27.3)
Early sepsis No. (%)	1 (20)	5 (11.9)	5 (6.8)	11 (9.1)
Surfactant (120 mg) use (No., Mean ± SD)	2.0 ± 0.7	1.4 ± 0.5	1.3 ± 0.5	1.4 ± 0.5
TPN duration (days, Mean ± SD)	78.6 ± 67.1	56.3 ± 37.2	47.8 ± 42.3	52.1 ± 41.9
Transfusion amount (unit, Mean ± SD)	21.4 ± 20.3	7.5 ± 4.5	6.1 ± 3.8	7.2 ± 6.2
O₂ therapy (days, Mean ± SD)				
Total duration	129.3 ± 35.2	114.1 ± 42.2	105.9 ± 61.4	109.6 ± 54.6
Mechanical ventilation	52.4 ± 25.2	45.0 ± 19.3	43.4 ± 47.8	44.3 ± 39.3
CPAP	51.4 ± 21.3	33.5 ± 31.5	41.0 ± 32.7	38.8 ± 32.0

AP-ROP, aggressive posterior retinopathy of prematurity; VSGA, very small for gestational age; SGA, small for gestational age; AGA, appropriate for gestational age; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; TPN, total parenteral nutrition; CPAP, continuous positive airway pressure.

Table 2. Onset and progression of retinopathy of prematurity (ROP) in worse eyes

Age	Onset of any ROP (n = 119)	Onset of type 1 ROP (n = 78)
Postmenstrual age (weeks)		
Mean	33.5 ± 1.9	36.1 ± 2.5
Median	33.3	35.9
Range	30.1-41.4	30.3-41.9
Postnatal age (weeks)		
Mean	9.5 ± 2.1	12.1 ± 2.6
Median	9.3	12.1
Range	5.7-18.3	6.1-17.1

shown in Table 1. Seventy-eight infants (64.5%) showed type 1 ROP, and laser treatment was performed in both eyes. Of the 121 infants, 17 (14.0%) infants with AP-ROP defined by revised IC-ROP were identified (Table 1) (12). Fourteen of 17 infants with AP-ROP showed vascularization in zone I, and others showed posterior zone II. Of the 17 infants with AP-ROP, 15 infants showed stage 3 ROP or less, but 2 infants developed bilateral stage 5 ROP.

In 6 (5.0%) of 121 infants, ROP was shown in at least one eye at the first screening examination performed between 29 to 31 weeks of PMA. Three infants had ROP stage 1, one had stage 2, and two had stage 3 at the first examination. The mean postnatal ages (PNAs) and PMAs at the onset of any stage of ROP and type 1 ROP in the worse eye are shown in Table 2. The mean PMAs at the onset of type 1 ROP in the worse eyes of infants with
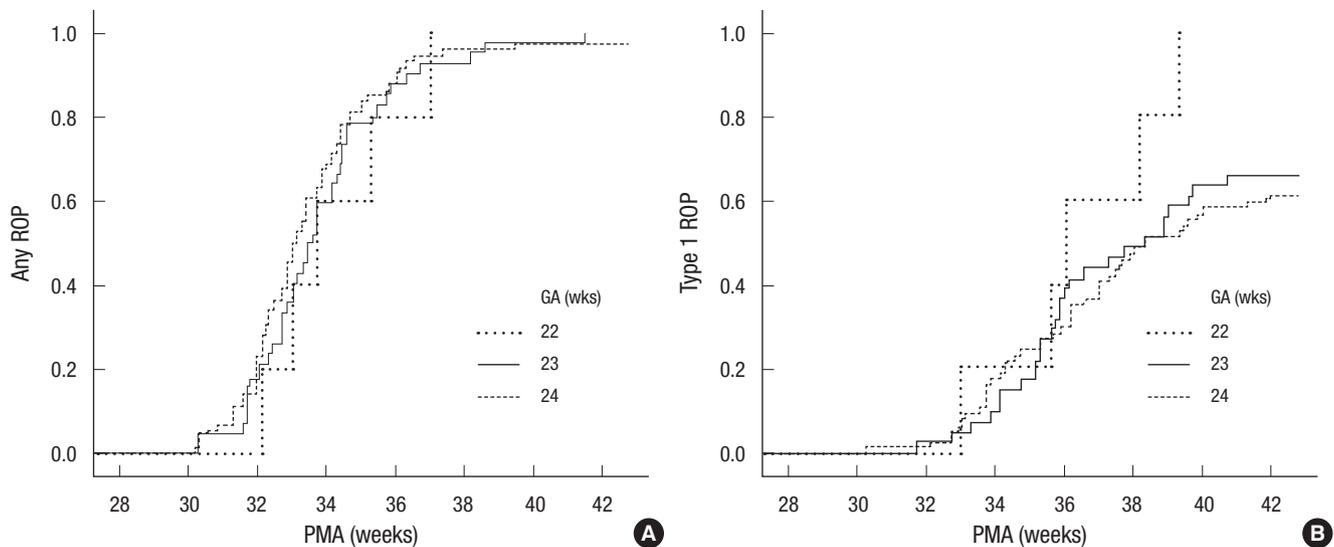
Fig. 2. Onset of any retinopathy of prematurity (ROP) (**A**) and type 1 ROP (**B**) in worse eyes relative to gestational age (GA) at birth. P = 0.769, 0.511, 0.566, the onset of any ROP between GA of 22 and 23, 22 and 24, and 23 and 24, respectively, P = 0.122, 0.062, 0.654, the onset of type 1 ROP between GA of 22 and 23, 22 and 24, and 23 and 24, respectively, log-rank test. PMA, postmenstrual age.

Table 3. Systemic and ocular risk factors for the development of type 1 retinopathy of prematurity (ROP) among infants born before 25 weeks gestation

Parameters	Type 1 ROP (n = 78)	No Type 1 ROP (n = 43)	P value
Gender, No. of male (%)	39 (50)	20 (46.5)	0.713
GA (mean ± SD)	24.0 ± 0.7	24.1 ± 5.7	0.282
Birth weight (mean ± SD)	643.2 ± 111.5	670.5 ± 104.2	0.281
SGA and VSGA, No. (%)	6 (7.7)	1 (2.3)	0.226
Multiple pregnancy, No. (%)	33 (42.3)	14 (32.6)	0.292
Apgar score (mean ± SD)			
1 min	4.0 ± 1.4	4.5 ± 1.5	0.052
5 min	6.7 ± 1.5	7.0 ± 1.2	0.176
PDA ligation, No. (%)	51 (65.4)	35 (81.4)	0.063
IVH ≥ grade 3, No. (%)	32 (41.0)	11 (25.6)	0.089
BPD ≥ moderate, No. (%)	51 (65.4)	27 (62.8)	0.775
NEC operation, No. (%)	13 (16.7)	7 (16.3)	0.956
Culture-proven sepsis, No. (%)	17 (21.8)	16 (37.2)	0.068
Early sepsis, No. (%)	5 (6.4)	6 (14.0)	0.167
TPN duration (days)	44.1 ± 34.8	66.5 ± 49.7	0.002*
Transfusion amount (unit)	7.7 ± 7.2	6.4 ± 3.7	0.292
O₂ therapy			
Mechanical ventilation (days)	43.1 ± 39.6	46.6 ± 39.0	0.537
CPAP (days)	37.6 ± 26.3	41.1 ± 40.7	0.475
Mechanical + CPAP (days)	80.6 ± 45.0	87.7 ± 70.1	0.391
Total (days)	108.5 ± 46.8	111.9 ± 66.6	0.647
Onset of any ROP (PMA)	33.2 ± 1.5	34.1 ± 2.4	0.012*
Onset of any ROP (PNA)	9.2 ± 1.7	10.1 ± 2.6	0.057

*P < 0.05. GA, gestational age; VSGA, very small for gestational age; SGA, small for gestational age; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; TPN, total parenteral nutrition; CPAP, continuous positive airway pressure; PMA, postmenstrual age; PNA, postnatal age.

Table 4. Risk factors for the development of type 1 ROP among infants born before 25 weeks gestation using multiple logistic regression analysis

Risk factors	P value	OR (95% CI)
Apgar score 1 min	0.309	0.850 (0.621-1.163)
PDA ligation	0.399	0.629 (0.215-1.846)
IVH ≥ grade 3	0.064	2.415 (0.949-6.144)
Culture-proven sepsis	0.141	0.481 (0.182-1.274)
TPN duration	0.132	0.991 (0.980-1.003)
Onset of any ROP (PMA)	0.136	0.836 (0.660-1.058)

OR, odds ratio; CI, confidence interval; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; TPN, total parenteral nutrition.

plan-Meier survival plots, the onset of any ROP and type 1 ROP were not significantly different between GA groups (Fig. 2). All but one infant developed type 1 ROP after 31 weeks PMA. One infant born at 24⁺¹ weeks gestation with an unstable clinical course showed zone I plus ROP at the first examination at 30⁺² weeks PMA.

Systemic factors and ROP progression in relation to type 1 ROP are shown in Table 3. The duration of TPN was significantly associated with the development of type 1 ROP (P = 0.002, t-test). The mean PMA at the onset of any stage of ROP was significantly shorter in patients with type 1 ROP than in others (P = 0.012, t-test). The 1-min Apgar score and mean PNAs at the onset of any stage of ROP were lower in type 1 ROP with borderline significance (P = 0.052 and 0.057, respectively, t-test). However, neither birth weight nor GA at birth was associated with the development of type 1 ROP in this cohort. Multiple logistic regression analysis was performed to identify systemic and ocular risk factors that had significant associations with the development of type 1 ROP (Table 4). The IVH ≥ grade 3 was associated with the development of type 1 ROP with borderline signif-

a GA of 22, 23, and 24 weeks were 36.4 ± 2.4 (range, 33⁺⁰-39⁺²), 36.2 ± 2.3 (range, 31⁺⁵-40⁺⁵), and 36.0 ± 2.6 weeks (range, 30⁺² -41⁺⁶), respectively. The onset of any ROP and type 1 ROP in the worse eye relative to GA at birth is summarized in Fig. 2. In Ka-

Table 5. Incidence of retinopathy of prematurity (ROP) in infants before 25 weeks' gestation compared with recent studies

Items	Present study	Sweden (13)	Germany (14)	Australia (15)	Scotland (16)	USA (17)
Study type	Single center	Population-based	Single center	Single center	Population-based	Single center
Study period	2004-2011	2004-2007	2001-2009	1992-2009	1990-2009	2003-2007
No. of infants						
GA 22-24 wk	121	157	125	147	72	79
GA 22 wk	5	5	13	NA	NA	NA
GA 23 wk	42	53	57	21	NA	NA
GA 24 wk	74	99	55	126	NA	NA
Any ROP (%)	98.4	87.9	NA	89.8	88.9	87
GA 22 wk	100	100	NA	NA	NA	NA
GA 23 wk	100	90.6	NA	90.5	NA	NA
GA 24 wk	97.3	85.9	NA	89.7	NA	NA
Severe ROP (%)*	67.8	54.8	29.6[†]	19.2	68.1	23[†]
GA 22 wk	100	80.0	61.5[†]	NA	NA	NA
GA 23 wk	61.9	62.3	24.6[†]	18.6	NA	NA
GA 24 wk	68.9	49.5	27.3[†]	18.3	NA	NA

*Stage 3 or more ROP; [†]laser-treated patients. NA, not available; GA, gestational age; wk, week.

icance (OR, 2.415; $P = 0.064$).

DISCUSSION

This study investigated the incidence and natural course of ROP in 121 extremely preterm infants born before 25 weeks gestation in a neonatal intensive care unit at a single medical center in Korea. The incidence of any ROP and type 1 ROP in this cohort was high, 98.4% and 64.5%, respectively. However, the incidence (5.0%) of stage 4 or 5 ROP was relatively low. Other studies on the incidence of ROP in extremely preterm infants also showed high incidences of any ROP, around 90% (Table 5) (13-17). However, compared with recent studies, our study showed higher incidence of severe ROP (Table 5) (13-17). Differences in the study design, definition of severe ROP, comorbidity of infants, proportion of inborn infants, and disagreement on plus sign may explain the reason (18). As GA at birth decreases, incidence of severe ROP usually increases (10, 11, 13, 14). However, in this study, the incidence of type 1 ROP was not significantly different between 23 and 24 weeks GA groups.

The natural course of ROP in this cohort showed a relatively early onset and progression compared to the ET-ROP study. The mean PMAs at the onset of any ROP and type 1 ROP were similar to those of a Swedish population-based study (19). Although only 5% of infants showed any ROP at ≤ 31 weeks PMA, one (0.8%) infant born at 24[+1] weeks' gestation developed type 1 ROP as early as 30[+2] weeks PMA. The development of type 1 ROP before 31 weeks PMA was not reported in two recent studies including more than 100 preterm infants born before 25 weeks gestation. In a German cohort study, no preterm infants required treatment before the 33rd postmenstrual week (14). In a Swedish study, ROP at stages 2 and 3 was seen as early as 29.9 and 31.6 weeks, respectively (19, 20). Thus, the authors recommend postponing the first examination until PMA of 31 weeks (20). For the infants born before 27 weeks gestation, British guide-

lines recommend that ROP screening should start at 30 to 31 weeks PMA, while American guidelines recommend the first screening to be performed at PMA of 31 weeks (7, 8). Although these current screening protocols are feasible for most preterm infants born before 25 weeks gestation, the results of this study suggest that screening at 30 weeks PMA may be necessary in these infants with an unstable clinical course.

The present study investigated systemic and ocular risk factors in relation to the development of type 1 ROP. In univariate analysis, a shorter duration of TPN was significantly associated with a higher incidence of type 1 ROP. A recent study about aggressive parenteral nutrition in preterm infants revealed the serum levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP3) were higher in aggressive parenteral nutrition group than those of conventional parenteral nutrition group and lower levels of IGF-I and IGFBP3 in conventional parenteral nutrition group were negatively correlated with development of ROP (21). Thus, shorter duration of TPN might affect the serum level of IGF-1 and IGFBP3, which might result in frequent development of type 1 ROP. However, the exact mechanism remains to be elucidated. In addition, an earlier onset of ROP was significantly related to a higher incidence of type 1 ROP. This finding is consistent with the Swedish population-based study, which revealed that PMA at the onset of ROP was significantly related to the severity of ROP (19). However, this finding is inconsistent with results of the CRYO-ROP study (22, 23). Differences in clinical characteristics, especially GA at birth, among the enrolled infants, may explain the inconsistency. In multiple logistic regression analysis, IVH ≥ grade 3 was associated with the development of type 1 ROP with borderline significance. This is consistent with the report that IVH was predictive of the development of ROP (24). In our study, previously reported risk factors including birth weight, multiple birth, and duration of oxygen therapy were not associated with type 1 ROP. In many studies including the ET-ROP and CRYO-

ROP studies, low birth weight was significantly associated with the development of severe ROP (22-24). In a German cohort study, the odds ratio for treatment increased by 1.22 per 100 g of decrease in body weight (14). However, in this study, birth weight was not associated with the development of type 1 ROP. This finding is consistent with a study by Teed and Saunders (17) study, which showed no association of birth weight with type 1 ROP in infants born before 25 weeks gestation. In addition, multiple births, which was associated with an increased risk of reaching threshold ROP in the CRYO-ROP study, and the duration of oxygen therapy, which was also associated with ROP in several studies, were not associated with type 1 ROP in this study (22, 25, 26). This may imply that risk factors for ROP may be more complex in extremely preterm infants born before 25 weeks gestation than in more mature infants, and other neonatal factors may contribute more to the development of severe ROP.

In conclusion, this study revealed the incidence, natural course, and risk factors of ROP in infants born before 25 weeks gestation in Korea. Although the incidence of ROP is very high, the proportion of infants with stage 4 or stage 5 ROP is relatively low when timely treatment is administered. Although rare, early onset of type 1 ROP before 31 weeks PMA is observed. Thus, earlier screening may be necessary in these extremely preterm infants with an unstable clinical course. Risk factors associated with an increased risk of type 1 ROP appear different in extremely preterm infants from those of more mature infants.

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