Retinopathy of Prematurity Among Very Low-Birth-Weight Infants in China: Incidence and Perinatal Risk Factors

Tian Wu,1 Li Zhang,1 Yu Tong,1,2 Yi Qu,1,2 Bin Xia,1,2 and Dezhi Mu1,2

1Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan Province, China
2Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of the Ministry of Education, Sichuan University, Chengdu, China

PURPOSE. Retinopathy of prematurity (ROP) is the leading cause of blindness in children worldwide. This study aimed to determine the incidence and perinatal risk factors for ROP in very low-birth-weight (VLBW) Chinese infants.

METHODS. A retrospective study of the medical records of 504 VLBW infants screened for ROP from 2012 to 2015 was performed in West China Second University Hospital. VLBW infants were examined according to the Royal College of Ophthalmologists ROP guideline and retinopathy was graded following the International Classification of ROP. Perinatal risk factors for ROP were assessed using univariate and multivariate analyses.

RESULTS. The overall incidence of ROP in our study was 26.0% (131/504). Stage 1 ROP, stage 2 ROP, and stage ≥3 ROP were detected in 17.5%, 5.4%, and 3.2% of the infants screened, respectively. In the univariate analysis, many perinatal risk factors were found to have a significant association with ROP. In the subsequent multivariate analysis, in vitro fertilization (IVF) (odds ratio [OR] = 1.896; 95% confidence interval [CI] 1.031–3.486), gestational age (GA) < 32 weeks (OR = 2.171; 95% CI 1.085–4.346), apnea (OR = 2.001; 95% CI 1.224–3.272), bronchopulmonary dysplasia (BPD) (OR = 5.098; 95% CI 2.307–11.265), sepsis (OR = 2.212; 95% CI 1.070–4.576), patent ductus arteriosus (PDA) (OR = 1.675; 95% CI 1.011–2.774), and blood transfusion (OR = 1.819; 95% CI 1.046–3.163) were independently associated with the development of ROP (all P < 0.05).

CONCLUSIONS. In VLBW Chinese infants, IVF, GA < 32 weeks, apnea, BPD, sepsis, PDA, and blood transfusion were independent perinatal risk factors for ROP. Keywords: retinopathy of prematurity, risk factors, very low birth weight, infants, Chinese

Correspondence: Dezhi Mu, Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China; mudz@scu.edu.cn.

Bin Xia, Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China; xiabin1972@163.com.

TW and LZ contributed equally to the work presented here and should therefore be regarded as equivalent authors.

Submitted: October 15, 2017
Accepted: January 3, 2018

Retinopathy of prematurity (ROP) is a vasoproliferative disorder that develops in the retina of infants born prematurely, and was first described in the year 1942 by Terry.1 With the improvement in the survival rate of premature infants in the last decade, the number of infants with ROP has increased worldwide.2 To date, ROP has been a leading cause of childhood blindness, particularly in the middle-income developing countries in Asia.3 Compared to developed countries, bigger and more mature infants in China also develop severe ROP, so early diagnosis and timely treatment are important for preventing the progression of ROP.4,5 Nevertheless, there are limited studies among preterm infants in China.

Over the years, immaturity and high concentration of oxygen therapy were previously thought to be important contributory factors to the development of ROP.6 However, not all premature infants develop ROP after prolonged exposure to supplementary oxygen. Several studies suggest that ROP is a multifactorial disease involving many prenatal and postnatal factors or neonatal therapies, such as maternal hypertension, multiple births, male sex, respiratory distress syndrome (RDS), apnea, sepsis, intraventricular hemorrhage (IVH), blood transfusions, and genetic factors.7–9 In many of these studies, the results were often controversial. The aim of this study was to analyze the potential perinatal risk factors for the development of ROP and the incidence among Chinese infants with birth weight less than 1500 g, to provide a framework for reducing the incidence of ROP.

METHODS

We performed a retrospective cohort study that analyzed collected data on very low-birth-weight (VLBW) infants who were admitted at West China Second University Hospital between June 1, 2012, and December 31, 2015. All the infants underwent eye examination for ROP. Exclusion criteria were infants with severe congenital or chromosomal anomalies, infants who died before eye examination, and infants with incomplete data. The study followed to the tenets of the Declaration of Helsinki. The study protocol was approved by the medical ethics committee of West China Second University Hospital, and written informed consent was obtained from the parents of the infants.

The infants were examined by ophthalmologists, using indirect ophthalmoscopy according to the Royal College of Ophthalmologists ROP guideline.10,11 The infants were first examined at 4 to 6 weeks after birth. Subsequently, routine reexamination was performed every week depending on the retinal findings. ROP was classified according to the International Classification of ROP including the stage, zone, and presence or absence of plus disease. The antenatal maternal
variables included maternal age, primigravidity, mode of delivery (cesarean or vaginal), singleton gestation, in vitro fertilization (IVF), gestational diabetes mellitus (GDM), pre-eclampsia (PE), intrahepatic cholestasis of pregnancy (ICP), preterm premature rupture of membranes (PPROM), chorioamnionitis, placenta previa, placental abruption, and antenatal steroid use. Neonatal risk factors included gestational age (GA), birth weight (BW), sex, apnea, RDS, bronchopulmonary dysplasia (BPD), pneumonia, sepsis, IVH, patent ductus arteriosus (PDA), acidosis, hypoglycemia, hyperglycemia, hyperbilirubinemia, invasive mechanical ventilation (MV), blood transfusions, and surfactant and dexamethasone administration.

Statistical analyses were performed using SPSS version 20 (SPSS, Inc., Chicago, IL, USA). Pearson’s χ² test and Fisher’s exact test were used to compare categorical variables. Independent sample t-test was used for continuous data. Continuous variables were expressed as means and standard deviation. Multivariate logistic regression analysis was performed to identify the independent risk factors for ROP. All tests of hypotheses were 2-tailed. Statistical significance was defined as a P value < 0.05.

RESULTS
During the study period, a total of 535 preterm infants were screened, of whom 16 (3.0%) died before completion of ROP screening and 15 (2.8%) had insufficient clinical information; these 31 (5.8%) infants were excluded. The remaining 504 eligible infants were included in the analysis. The mean estimated GA of the infants was 30.6 ± 2.3 weeks, the mean birth weight was 1251.7 ± 185.1 g, and the sex distribution was 261 (51.8%) male and 243 (48.2%) female.

Distribution of Incidence of ROP
ROP of any stage was found in 131 (26.0%) infants: 94 had zone III disease, 27 had zone II disease, and 5 had zone I disease; 88 had stage 1 (67.2%), 27 had stage 2 (20.6%), 11 had stage 3 (8.4%), 5 had aggressive posterior ROP (3.8%); none of the neonates presented ROP at stage 4 or 5. The analysis by GA showed that the incidence rates of ROP and stage 1 ROP were 30.5% and 20.4% in infants with GA < 32 weeks, significantly higher than in infants with GA ≥ 32 weeks (13.9% and 9.5%, respectively). The analysis by BW showed that the incidence rates of stage 2 ROP and stage ≥ 3 ROP among infants with BW < 1000 g were higher than that among infants with BW ≥ 1000 g (P < 0.05) (Table 1).

Maternal and Neonatal Risk Factors for ROP
Univariate and multivariate analyses were conducted to identify the factors associated with ROP and the results are summarized in Table 2. We found that increased rate of IVF was associated with the development of ROP (P < 0.05), and maternal ICP was lower among infants with ROP than in infants without ROP (P < 0.05). However, there were no differences in maternal age, primigravidity, cesarean delivery, singleton gestation, GDM, PE, PPROM, chorioamnionitis, placenta previa, placentation abnormality, and antenatal steroid use. We then analyzed neonatal factors contributing to ROP. The mean GA and BW in infants with ROP (29.7 ± 1.9 weeks, 1209.0 ± 186.1 g) were significantly lower than in those without ROP (30.9 ± 2.3 weeks, 1266.7 ± 182.7 g) (P < 0.05). GA < 32 weeks, male sex, apnea, RDS, BPD, sepsis, PDA, and hyperglycemia were found to be statistically associated with ROP (P < 0.05).

Statistical analyses were performed using SPSS version 20 (SPSS, Inc., Chicago, IL, USA). Pearson’s χ² test and Fisher’s exact test were used for continuous data. Continuous variables were expressed as means and standard deviation. Multivariate logistic regression analysis was performed to identify the independent risk factors for ROP. All tests of hypotheses were 2-tailed. Statistical significance was defined as a P value < 0.05.

IVF was the only prenatal risk factor for ROP, so we further analyzed the characteristics of infants with IVF (Table 3). Compared to infants without IVF, the mean maternal age and the rates of multiple birth and stage 1 ROP were significantly higher, but the mean GA and the rate of maternal age < 25 years old were lower among infants with IVF (P < 0.05). The mean BW was not statistically different between the two groups. After multivariable adjustments, IVF (odds ratio [OR] = 1.896; 95% confidence interval [CI] 1.031–3.486), GA < 32 weeks (OR = 2.171; 95% CI 1.085–4.346), apnea (OR = 2.001; 95% CI 1.224–3.272), BPD (OR = 5.098; 95% CI 2.307–11.265), sepsis (OR = 2.212; 95% CI 1.070–4.576), PDA (OR = 1.675; 95% CI 1.011–2.774), and blood transfusion (OR = 1.819; 95% CI 1.046–3.163) were independently associated with the development of ROP (all P < 0.05).

Maternal and Neonatal Characteristics According to the Staging of ROP
According to the staging of ROP, we divided infants with ROP into three groups and analyzed their characteristics (Table 4). Compared to infants without ROP, the rate of IVF was higher only in infants with stage 1 ROP; the rate of maternal age between 30 and 35 years old was higher only in infants with stage 2 ROP (P < 0.05). The mean GA of ROP, regardless of any severity, was lower than that of the no-ROP group, and the lowest mean GA was 29.0 ± 1.9 weeks in infants with stage 2 ROP. The mean BW was lower among infants with ROP of any stage; the rates of RDS and hyperglycemia were higher among infants with stage 1 ROP and stage ≥ 3 ROP; the rates of dexamethasone use and invasive MV were higher in infants with stage 1 ROP and stage ≥ 3 ROP; the rates of dexamethasone use and invasive MV were higher among infants with stage 1 ROP and stage ≥ 3 ROP; the rates of BPD and dexamethasone use (P < 0.05).

There was no statistical difference between the stage 2 ROP group and the stage ≥ 3 ROP group.
Table 2. Univariate and Multivariate Analysis of Risk Factors for ROP in VLBW Infants [n (%)]

<table>
<thead>
<tr>
<th>Variables</th>
<th>No ROP, n = 375</th>
<th>ROP, n = 131</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–30</td>
<td>163 (43.7)</td>
<td>52 (39.7)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;25</td>
<td>61 (16.4)</td>
<td>14 (10.7)</td>
<td>0.328</td>
<td>0.719</td>
</tr>
<tr>
<td>30–35</td>
<td>90 (24.1)</td>
<td>46 (35.1)</td>
<td>0.051</td>
<td>1.602</td>
</tr>
<tr>
<td>&gt;35</td>
<td>59 (15.8)</td>
<td>19 (14.5)</td>
<td>0.976</td>
<td>1.009</td>
</tr>
<tr>
<td><strong>Primigravity</strong></td>
<td>125 (33.5)</td>
<td>44 (33.5)</td>
<td>0.643</td>
<td>0.904</td>
</tr>
<tr>
<td><strong>Cesarean delivery</strong></td>
<td>200 (53.6)</td>
<td>64 (48.9)</td>
<td>0.292</td>
<td>0.807</td>
</tr>
<tr>
<td><strong>Singletons</strong></td>
<td>208 (55.8)</td>
<td>65 (49.6)</td>
<td>0.242</td>
<td>0.788</td>
</tr>
<tr>
<td><strong>IVF</strong></td>
<td>58 (15.5)</td>
<td>40 (30.5)</td>
<td>0.000</td>
<td>2.387</td>
</tr>
<tr>
<td><strong>Dexamethasone use</strong></td>
<td>101 (26.3)</td>
<td>25 (19.1)</td>
<td>0.101</td>
<td>0.662</td>
</tr>
<tr>
<td><strong>Surfactant use</strong></td>
<td>136 (36.5)</td>
<td>77 (58.8)</td>
<td>0.530</td>
<td>1.168</td>
</tr>
<tr>
<td><strong>Hyperbilirubinemia</strong></td>
<td>123 (33.0)</td>
<td>45 (34.4)</td>
<td>0.774</td>
<td>1.086</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>93 (24.9)</td>
<td>35 (26.7)</td>
<td>0.687</td>
<td>1.098</td>
</tr>
<tr>
<td><strong>Acidosis</strong></td>
<td>115 (30.8)</td>
<td>44 (33.6)</td>
<td>0.448</td>
<td>1.179</td>
</tr>
<tr>
<td><strong>PDA</strong></td>
<td>91 (24.4)</td>
<td>45 (34.4)</td>
<td>0.292</td>
<td>0.807</td>
</tr>
<tr>
<td><strong>IVH</strong></td>
<td>272 (72.9)</td>
<td>104 (79.4)</td>
<td>0.255</td>
<td>1.346</td>
</tr>
<tr>
<td><strong>BPD</strong></td>
<td>22 (5.9)</td>
<td>11 (8.4)</td>
<td>0.136</td>
<td>1.808</td>
</tr>
<tr>
<td><strong>Antenatal steroids</strong></td>
<td>194 (52.0)</td>
<td>73 (55.7)</td>
<td>0.235</td>
<td>1.314</td>
</tr>
<tr>
<td><strong>Placental abruption</strong></td>
<td>18 (4.8)</td>
<td>11 (8.4)</td>
<td>0.666</td>
<td>1.175</td>
</tr>
<tr>
<td><strong>Chorioamnionitis</strong></td>
<td>73 (19.6)</td>
<td>29 (22.1)</td>
<td>0.530</td>
<td>1.168</td>
</tr>
<tr>
<td><strong>PPROM</strong></td>
<td>146 (39.1)</td>
<td>56 (42.7)</td>
<td>0.469</td>
<td>1.161</td>
</tr>
<tr>
<td><strong>Chorioamnionitis</strong></td>
<td>73 (19.6)</td>
<td>18 (14.1)</td>
<td>0.101</td>
<td>0.662</td>
</tr>
<tr>
<td><strong>Placenta previa</strong></td>
<td>27 (7.2)</td>
<td>11 (8.4)</td>
<td>0.666</td>
<td>1.175</td>
</tr>
<tr>
<td><strong>Placental abruption</strong></td>
<td>18 (4.8)</td>
<td>11 (8.4)</td>
<td>0.666</td>
<td>1.175</td>
</tr>
<tr>
<td><strong>Antenatal steroids</strong></td>
<td>194 (52.0)</td>
<td>73 (55.7)</td>
<td>0.235</td>
<td>1.346</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Distribution of ROP in VLBW Infants

The incidence of ROP of any stage among VLBW infants varies in different countries, and has been reported to range from 10% to 34% in Europe and America, while our study showed an incidence of 26.0% in VLBW Chinese infants. Our findings were consistent with a study from Singapore by Shah et al. that reported an incidence of 29.2%. In our study, the incidence of ROP among VLBW infants with GA < 32 weeks was 30.5%, similar to the incidence reported in Saudi Arabia (37.4%) by Binkhathlan et al. The incidence of stage 3+ ROP in our study was 3.2%, significantly higher in infants delivered at < 32 weeks or with BW < 1000 g and consistent with the findings of other Chinese studies. Moreover, no infant had stage 4 or stage 5 ROP in our study. With the increased awareness of the risk of blindness caused by ROP, the Chinese Ministry of Health guidelines for the prevention and treatment of ROP were published in 2004. Strict indications and reasonable concentration and time of oxygen inhalation are the most important measures to prevent VLBW infants from developing severe ROP. Otherwise, laser photocoagulation or cryocoagulation is performed within 72 hours after diagnosis of threshold ROP in any zone or prethreshold ROP in zone I.

Maternal Obstetric Factors and ROP

In our study, maternal obstetric factors such as IVF, PE, ICP, and others were studied. However, only IVF showed a statistically significant correlation with ROP. After adjusting for confounding factors, IVF increased the risk of ROP by approximately
Blood transfusions 148 (39.7) 60 (68.2)* 25 (92.6)†§ 11 (68.8)‡ 0.000
Invasive MV 94 (25.2) 29 (33.3) 14 (51.9) 7 (43.8)‡ 0.003

Dexamethasone use 18 (4.8) 9 (10.2) 6 (22.2)† 7 (43.8)‡
Hyperbilirubinemia 123 (33.0) 33 (37.5) 8 (29.6) 4 (25.0) 0.737
Hyperglycemia 28 (7.5) 14 (15.9)* 3 (11.1) 4 (25.0)‡ 0.014
Hypoglycemia 93 (24.9) 23 (26.1) 7 (25.9) 5 (31.3) 0.948
Acidosis 115 (30.8) 34 (38.6) 6 (22.2) 4 (25.0) 0.355
Pneumonia 288 (77.2) 68 (77.8) 23 (85.2) 12 (75.0) 0.838
Sepsis 29 (7.8) 12 (13.6) 7 (25.9)† 2 (12.5) 0.012
IVH 272 (72.9) 70 (79.6) 21 (77.8) 13 (81.3) 0.577
PDA 91 (24.4) 42 (47.7)* 15 (55.6)† 8 (50.0)‡ 0.000
Antenatal sterols 194 (52.0) 50 (56.8) 15 (55.6)† 8 (50.0)‡ 0.000

Maternal age, y
<25 61 (16.4) 10 (11.4) 2 (7.4) 2 (12.5) 0.499
25–30 163 (43.7) 37 (42.0) 9 (33.3) 6 (37.5) 0.726
30–35 90 (24.1) 29 (33.3) 12 (44.4)† 5 (31.3) 0.059
>35 59 (15.8) 12 (13.6) 4 (14.8) 3 (18.8) 0.925

Primigravida 125 (33.5) 28 (31.8) 10 (37.0) 3 (18.8) 0.649
Cesarean delivery 200 (53.6) 45 (51.1) 14 (51.9) 5 (31.3) 0.369
Singleton 208 (55.8) 46 (52.5) 13 (48.2) 6 (37.5) 0.441

IVF 58 (15.5) 27 (30.7)* 8 (29.6) 5 (31.3) 0.003
Diabetes 96 (25.7) 23 (26.1) 7 (25.9) 5 (31.3) 0.190
PE 101 (26.3) 15 (17.0) 5 (18.5) 4 (25.0) 0.843
ICP 44 (11.8) 6 (6.8) 0 (0.0) 1 (6.3) 0.136
PPROM 146 (39.1) 36 (40.9) 13 (48.2) 7 (43.8) 0.000

Maternal age, y
<25 30.9 ± 2.3 29.9 ± 1.7* 29.0 ± 1.9† 29.4 ± 2.2‡ 0.000
25–30 163.7 ± 182.7 122.5 ± 172.3 117.8 ± 210.9† 117.0 ± 215.0‡ 0.009

BW, g
Male 182 (48.8) 50 (56.8) 18 (66.7) 11 (68.8) 0.911
Female 137 (36.7) 49 (55.7) 20 (74.1) 12 (75.0) 0.000
RDS 141 (37.8) 51 (58.0)† 14 (51.9) 11 (68.8)‡ 0.001
BPD 22 (5.9) 22 (25.0)* 15 (55.6)† 8 (50.0)‡ 0.000

Pneumonia 28 (7.5) 14 (15.9)* 3 (11.1) 4 (25.0)‡ 0.014
SIH 29 (7.8) 12 (13.6) 7 (25.9)† 2 (12.5) 0.012
IVH 272 (72.9) 70 (79.6) 21 (77.8) 13 (81.3) 0.577
PDA 91 (24.4) 42 (47.7)* 15 (55.6)† 8 (50.0)‡ 0.000
Acidosis 115 (30.8) 34 (38.6) 6 (22.2) 4 (25.0) 0.355
Hypoglycemia 93 (24.9) 23 (26.1) 7 (25.9) 5 (31.3) 0.948
Hyperglycemia 28 (7.5) 14 (15.9)* 3 (11.1) 4 (25.0)‡ 0.014
Hyperbilirubinemia 123 (33.0) 33 (37.5) 8 (29.6) 4 (25.0) 0.737
Surfactant use 136 (36.5) 51 (58.0)* 15 (55.6)† 11 (68.8)‡ 0.000
Dexamethasone use 18 (4.8) 9 (10.2) 6 (22.2) 7 (43.8)‡ 0.000
Invasive MV 94 (25.2) 29 (33.3) 13 (48.2) 9 (56.3)‡ 0.003

Blood transfusions 148 (39.7) 60 (68.2)* 25 (92.6)‡ 11 (68.8)‡ 0.000

* P < 0.05 between groups with no ROP and stage 1 ROP; univariate analysis.
† P < 0.05 between groups with no ROP and stage 2 ROP; univariate analysis.
‡ P < 0.05 between groups with no ROP and stage 3 ROP; univariate analysis.
§ P < 0.05 between groups with stage 1 ROP and stage 2 ROP; univariate analysis.
|| P < 0.05 between groups with stage 1 ROP and stage 3 ROP; univariate analysis.

Neonatal Factors and ROP
It is well known that low GA and BW are both strong predictors of ROP. In our study, the mean GA was 29.7 weeks among infants with ROP, significantly lower than that among...
infants without ROP. When GA was less than 32 weeks, the risk of ROP doubled. Low GA might reflect the immaturity of retina at birth and the retinal vulnerability to injury. Furthermore, immature GA could increase infants’ exposure to adverse extraterine factors (i.e., oxygen and infection) contributing to the risk of ROP. The mean GA was the lowest in infants with stage 2 ROP, so the rates of their BPD, sepsis, and blood transfusion were also the highest. Moreover, we did not find that BW < 1000 g was an independent risk factor for ROP. All of our subjects were VLBW infants, so the impact of BW on ROP was not significant.

Various studies have reported that neonatal respiratory disease and related treatments are closely related to the occurrence of ROP. In this study, the risk of ROP development was five times higher in infants with BPD, similar to the findings by Gebeşte et al. (OR = 5.952; 95% CI 2.050–17.447). Also, BPD was found to be the most powerful risk factor for the development of ROP and a strong predictor of the severity of ROP in our study. The lungs of VLBW infants are usually immature, and so they most often require continuous oxygen treatment for a period of time, sometimes at high oxygen concentrations. In vitro tests have shown that the immature retina is extremely sensitive to high concentrations of oxygen, which is the major cause of vasoconstriction of immature vessels. After stopping oxygen inhalation, the retinal tissue will be hypoxic due to vasoconstriction, which can lead to the upregulation of VEGF. VEGF can stimulate retinal angiogenesis and plays an important role in the pathogenesis of ROP. Moreover, some studies have reported that significant changes in blood oxygen saturation resulting from apnea and oxygen therapy can also increase the risk of ROP through the above mechanism. In our study, apnea was an independent risk factor for ROP.

Several studies have implicated infection in the development of ROP. A systematic review and meta-analysis of eight studies indicated that systemic fungal infection was closely related to the occurrence of any stage of ROP in VLBW infants. Lundgren et al. reported that multiple infectious episodes, including sepsis, C-reactive protein level > 10 mg/L, and other clinical signs of infection, were associated with aggressive posterior ROP. In our logistic regression analysis, the risk of ROP in VLBW infants with sepsis doubled. The effects of infection on the retina have been reported. A possible explanation could be that systemic proinflammatory cytokines might exert a direct effect on retinal neovascularization via inflammation-regulated VEGF production. Liu et al. indicated that hypotension and fluctuation of oxygen saturation following sepsis might affect the retinal perfusion and lead to retinal ischemia. Thus, the contribution of sepsis to the development of ROP is reasonable and deserves more attention.

Similar to other studies, PDA was an independent risk factor of ROP in this study. Mitsiakos and Papageorgiou reported that hemodynamic instability, brought about by open ductus arteriosus, and the more prolonged ventilatory support were both involved in the occurrence of ROP. While Tsui et al. indicated that PDA was closely related to BPD and blood transfusions, which may explain its impact on ROP. Furthermore, indomethacin for the treatment of PDA may also contribute to the occurrence of ROP. Beharry et al. found that indomethacin could influence retinal neovascularization through a VEGF-driven pathway in animal models. In our study, PDA was mainly associated with early-stage ROP. This may be related to the timely treatment of PDA in the early days after birth.

It is interesting to note that male sex was significantly associated with ROP in the univariate analysis (OR = 1.612; 95% CI 1.075–2.415) and in the multivariate analysis (OR = 1.606; 95% CI 0.988–2.612). Previous studies have shown that male sex is associated with worse respiratory outcomes, such as RDS and BPD, as well as IVH and ROP. Lingappan et al. thought that hormonal, physiological, and developmental differences between males and females might lead to sex-specific outcomes; recently, there have been fewer studies on this topic. The effects of sex difference on fetal and later infant retinal vascularization need further evaluation.

Neonatal Treatments and ROP

Accumulating evidence indicates that ROP is a disease caused by multiple factors, including treatment measures after birth. In our multivariate analysis, we found that blood transfusion was an independent risk factor for ROP. Since blood transfusion was first proposed as a risk factor for ROP, several studies in this regard have been conducted. Different hypotheses have been proposed to explain this association: (1) Blood transfusion of preterm infants with adult-type hemoglobin having a lower oxygen affinity causes excess oxygen release in the retinal tissue; (2) due to low levels of plasma transferrin and immature antioxidant systems in preterm infants, iron overload after transfusions will catalyze reactive oxygen species reactions and form free oxygen radicals. Free oxygen radicals can cause lipid peroxidation, DNA damage, and ROP by attacking membrane phospholipids. On the other hand, in most of the recent studies, blood transfusion has no longer been associated with the development of ROP after multivariate logistic regression analyses, possibly due to the fact that other concurrent risk factors placed these infants in the high-risk group. Therefore, it is very important to adjust the relationship between complex risk factors in future studies.

In this study, postnatal dexamethasone use was significantly higher among infants with ROP, especially those with stage ≥ 2 ROP, but there was no association between them in the multivariate analysis, consistent with previous studies. The mean GA among infants with ROP was significantly lower than that among those without ROP. Therefore, it is reasonable that those smaller infants were more vulnerable to illness and required dexamethasone, mechanical ventilation, and other treatments. However, some studies have reported contrary findings. A protective effect of dexamethasone on the severity of ROP was observed by Higgins et al. There are no clinical studies proving this hypothesis. Only animal models showed that steroids could inhibit preretinal and subretinal neovascularization. Also, Haroon Parupia and Dhanireddy reported that postnatal steroid use was an independent risk factor for severe ROP, and it may be associated with a high risk of fungal infection among infants who undergo treatment with dexamethasone. These controversial results may be attributable to the adjustment of different risk factors and different timing and courses of dexamethasone use.

Limitations

Our study had its limitations. First, our sample size was relatively small and cannot be generalized to all VLBW infants born in China. Second, our data were inconsistent due to the retrospective nature of this study, although we made efforts to exclude infants with incomplete clinical data. Nevertheless, this study provides important data on the incidence and risk factors of ROP in the Chinese population using strict ROP screening guidelines. This serves as a basis for future prospective multicenter trials.
CONCLUSIONS

In summary, the prevalence of ROP was found to be 26.0% in this study. The progression of ROP was influenced by many perinatal factors, such as IVF, GA < 32 weeks, apnea, BPD, sepsis, PDA, and blood transfusion. The mechanisms underlying the increased occurrence of ROP related to IVF, male sex, and other factors are not clear. Large-scale, prospective studies are required for further assessment.

Acknowledgments

Supported by the National Science Foundation of China (No. 813530016, 81630038, 81771634), the Major State Basic Research Development Program (2017YFA0104200), grants from Science and Technology Bureau of Sichuan Province (2014SZ0149, 2016TD0002), grants from Ministry of Education of China (IRT 0955), and a grant from the Clinical Discipline Program (Neonatology) from the Ministry of Health of China (1311200005303).

Disclosure: T. Wu, None; L. Zhang, None; Y. Tong, None; Y. Qu, None; B. Xia, None; D. Mu, None

References


