Scientific Research Publishing

Yangtze Medicine, 2022, 6, 95-113
https://www.scirp.org/journal/ym
ISSN Online: 2475-7349
ISSN Print: 2475-7330

Clinical Study on Pathogenic Factors and Screening Strategies of Retinopathy of Prematurity

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How to cite this paper: Naqvi, S.M.A.S., Mohammed, S., Ye, H. and Zhang, Y.F. (2022) Clinical Study on Pathogenic Factors and Screening Strategies of Retinopathy of Prematurity. *Yangtze Medicine*, **6**, 95-113.
https://doi.org/10.4236/ym.2022.64010

Received: August 25, 2022
Accepted: October 10, 2022
Published: October 13, 2022

Abstract

Objective: To investigate the incidence of retinopathy of prematurity (ROP), analyze the risk factors of ROP, and put forward effective screening strategies, to reduce its incidence. **Background:** Retinopathy of prematurity (ROP) is an eye disease that can happen in new born premature (born early) babies or have weigh less than 3 pounds at birth. ROP happens when abnormal blood vessels grow in the retina. There are multiple risk factors, which are causing the ROP. In our study we will analyses the risk factors of ROP. **Methods**: From February 2016 to August 2021, 190 premature infants in the neonatal intensive care unit (NICU) who received inpatient care and ophthalmic screening was selected as study subjects. ROP group (n = 32) and non-ROP group (n = 158) were selected, and the clinical data of the two groups were compared. Including oxygen concentration, mechanical ventilation, broncho pulmonic dysplasia, delivery mode (cesarean section, vaginal delivery), blood transfusion, anemia, gestational diabetes, gestational hypertension, fetal distress, preterm birth weight, gestation age, etc. Women were divided into two groups according to whether they had gestational diabetes mellitus (GDM) or not: gestational diabetic (n = 38) and non-gestational diabetics (n = 152). Age, pregnancy times, birth times, oxygen inhalation, birth weight, and gestational age were compared between the two groups. The X^2 test for counting data and the t-test for measuring data are then conducted according to the distribution characteristics of the data, The correlation analysis between ROP and

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a single risk factor was performed by chi-square test, and the analysis of the correlation between many risk factors and ROP was conducted by Logistic regression analysis. **Results**: 1) The incidence of ROP in the GDM group was higher than that in the non-GDM group ($P < 0.05$). 2) Gestational age and birth weight in gestational diabetes mellitus were slightly higher than those in non-gestational diabetic group. But there was no difference in gestational age, birth weight, birth times, gestational times, and age between the two groups ($P > 0.05$). 3) Univariate analysis showed that oxygen use, birth weight, gestational age, bronchopulmonary dysplasia, pregnancy-induced hypertension, and fetal distress in the ROP group and non-ROP group were statistically significant ($P < 0.05$). There was no difference in gender, mechanical ventilation, maternal age, and delivery mode between the two groups ($P > 0.05$). 4) Logistic multivariate analysis showed that oxygen use, gestational hypertension, diabetes mellitus during pregnancy, fetal distress, bronchopulmonary dysplasia, birth weight, and gestational age were the main risk factors for ROP. **Conclusion:** 1) Gestational diabetes mellitus is a high-risk factor for ROP. 2) Oxygen inhalation, birth weight, and gestational age are related to the occurrence and development of ROP. 3) In determining the initial screening time for ROP.

Keywords

Gestational Diabetes Mellitus, Retinopathy of Prematurity, Gestational Age, Birth Weight, Oxygen

1. Introduction

Retinopathy of prematurity (Retinopathy of Prematurity, ROP) as low birth weight or immature weight of retinal-related proliferative lesions, its main characteristics for the formation of neovascularization and retinal ischemia, at the same time can further lead to retinal detachment, degeneration, even secondary glaucoma, concurrent cataract, amblyopia, and strabismus, in serious cases, can also lead to children with blindness [1]. For the pathogenesis of ROP, the current medical community is generally recognized by the oxygen-free radical theory and cell molecule theory. It is found that multiple cytokines can affect the occurrence of neovascularization, and these cytokines can be divided into two types, respectively, non-oxygen-related factors and oxygen-related factors, among which the former is more common is IGF-1, while the latter is representative. Because the retina is rich in phospholipids and is highly sensitive to oxygen radicals, there is literature [2]. It is reported that the large fluctuation range of blood oxygen can generate large amounts of oxygen free radicals, leading to retinopathy in animal models, and the retinal range of avascular areas can be reduced in the first phase of development. In a relatively hypoxia or high oxygen environment, the body produces a large number of oxygen radicals, and at the same time, because the functions of premature infants are not fully developed, oxygen radicals cannot be removed in time, resulting in retinal ischemia and retinal vascular damage. In

the early fetus, arteries from the choroid and vitreous provide nutrients for the development of the retina, when the embryo diameter is >100 mm, small vitreous vessels pass through the optic disc, and when small branches extend from the optic disc to the peripheral retina. In the early stage of this stage, only the nerve fiber layer is seen, and the later small branches can reach deep into the interior. In general, the fetal retinal vessels begin to develop at 16 w, at 32 w at the nasal edge, and at 40 - 44 w after birth. If the fetus is born early at this stage, his retinal development is not perfect at this time. The temporal retina of premature infants shows vascularization and the relatively high oxygen environment after birth further contracts the retinal vessels of premature infants or even blocks. At the same time, because of hypoxia at this time, the body produces vascular proliferation factor, which stimulates retinal blood vessels and promotes angiogenesis. The appearance of neonatal blood vessels further leads to a series of pathological changes such as mechanization, bleeding, and exudation, which lays the pathophysiological foundation for the occurrence of ROP. Studies have found that retinal blood vessels develop through the inner boundary membrane to the optic web because of hyperplastic proliferation. The membrane surface and deep into the vitreous body, and then exudation and vitreous vascular mechanization, and then after the crystal, there will be connective tissue membrane formation, when the situation is serious, under the action of traction will lead to retinal detachment, thus appear Blind, which will greatly reduce the long-term quality of life of children There are many opinions on the relevant high-risk factors for ROP, and different results come from different studies. The existing consensus is gestational age (gestational age, GA) and low birth weight (birth weight, BW) is the two risk factors for ROP, in addition, to placental abruption, maternal pregnancy preeclampsia, intrauterine distress, anemia, neonatal hypoxic-ischemic encephalopathy, neonatal hyperbilirubinemia, and multiple pregnancies, and many other factors have a certain association with ROP, but currently both international or our domestic have no unified conclusion. In gestational women, gestational diabetes mellitus, and gestational hypertension are the more common complications, Pivodic Aldina [3]. In the study, gestational diabetes and hypertension were independent risk factors for ROP. Clinical research data show that in pregnant women with pregnancy hypertension, their systemic arterioles will undergo spastic contraction. Related studies found that pregnant women with pregnancy hypertension are prone to endovascular embolism, thus reducing blood volume, and further damage to the function of the placenta, the occurrence of this situation, will greatly reduce fetal growth of necessary nutrients and oxygen, thus hindering its normal growth, lead to intrauterine distress, low weight and premature birth [4] [5]. Such as in the literature report pointed out that in gestational diabetes patients, because the body a long time high blood sugar levels, hyperglycemia can induce vascular lesions, increase the risk of hypertension in gestational diabetes children, further affect the fetal oxygen, and the outcome is to delay fetal growth and development [6] [7].

To sum up, there are many international and domestic studies on the analysis

of risk factors related to ROP, but there is no unified conclusion, so it is particularly important to analyze the high-risk factors of ROP in the current region. Therefore, through a retrospective analysis of the detection of retinopathy of prematurity (ROP) in our hospital in the past five years, the birth quality, gestational age, oxygen concentration and time, and mechanical ventilation were recorded in detail. The clinical data of qi and bronchopulmonary dysplasia, further analyzed the clinical characteristics of ROP, and selected the corresponding risk factors through univariate analysis of several clinical factors and multivariate Logistic regression. And explore the appropriate screening strategies for retinopathy of prematurity suitable for the neonatal intensive care unit in the region, so as not to avoid missed diagnosis and increase the pain and family and social and economic burden of the children.

2. Materials and Methods

2.1. General Information

This paper retrospectively analyzed 190 premature infants who received inpatient monitoring and ophthalmological screening in the neonatal intensive care unit (NICU) of our hospital from February 2016 to August 2021 as the research objects. According to the results of ROP screening, they were divided into the ROP group and non-ROP group, including 32 cases in the ROP group and 158 cases in the non-ROP group. At the same time, to clarify the influencing factors of gestational diabetes on ROP, children were divided into gestational diabetes groups and non-gestational diabetes groups according to whether their mothers had gestational diabetes during pregnancy and obstetric examination. Among them, 38 cases in the gestational diabetes group were non-gestational diabetes mellitus. Group of 152 cases.

2.2. Diagnosis, Inclusion, and Exclusion Criteria

2.2.1. Diagnostic Criteria

Diagnostic criteria for gestational diabetes: the diagnostic criteria for gestational diabetes were formulated according to the "China Guidelines for the Prevention and Treatment of Type 2 Diabetes (2017 Edition)" formulated by the Diabetes Branch of the Chinese Medical Association. Time for 75 g OGTT, OGTT 2 h blood sugar is 8.5 - 11.1 mmol/L; fasting blood sugar is 5.1 - 7.0 mmol/L, one of the above blood sugar values can be diagnosed as GDM.

ROP diagnostic criteria: ROP was diagnosed and staged regarding the International Classification of ROP. In the International Classification of ROP (ICROP), the retina can be divided into 3 regions. Zone I: take the optic disc as the center, draw a circle with twice the distance from the optic disc to the fovea of the macula as the radius, and the area inside the circle is the zone I; zone II: draw a circle from zone I to the periphery of the retina on the nasal side, this annular area Zone II; Zone III: the remaining temporal meniscus beyond zone II is zone III, where ROP occurs most often. The most severe ROP occurred in zone I, and the mildest in zone III. Most lesions occurred in zone III,

followed by zone II.

2.2.2. Inclusion Criteria

1) Low birth weight infants and premature infants with a gestational age of ≤34 weeks or a birth weight of ≤2000 g; 2) singleton pregnancy; 3) complete preservation of clinical data; 4) successful neonatal survival after birth; 5) family members were informed about the study and signed the informed consent; 6) met the diagnostic criteria in the Guidelines for the Prevention and Treatment of Preterm Infants with Oxygen and Retinopathy.

2.2.3. Exclusion Criteria

1) Those with missing clinical data or lost to follow-up; 2) those with severe congenital chromosomal deletions or abnormalities; 3) those who died before eye screening; 4) those whose family members were unwilling to participate in the researcher; 5) eye structure Developmental abnormalities; 6) congenital malformations.

3. Method

3.1. Data Collection Method

Clinical data of mothers and preterm infants were collected, including oxygen concentration, mechanical ventilation, bronchopulmonary dysplasia, mode of delivery (cesarean section, vaginal delivery), blood transfusion, anemia, gestational diabetes mellitus, gestational hypertension, fetal distress, maternal age, birth weight of premature infants and gestational age at birth. At the same time, the fetuses were screened at 4 weeks after birth, or their gestational age was corrected to 32 weeks to carry out screening, and then based on the "China Guidelines for Retinopathy of Prematurity Screening" as the basic basis, they were divided into no ROP group and ROP group. According to the international classification of ROP: 1) the demarcation line between the intraretinal vascular area and the non-vascular area is obvious in stage 1; 2) there is a crest-like eminence within the demarcation line in stage 2; fibroid hyperplasia or new blood vessels can be seen; 4) retinal detachment in stage 4; 5) complete retinal detachment in stage 5.

3.2. Screening Methods

If preterm infants meet the screening criteria and sign a screening agreement, the screening will begin. 60 minutes before the examination, use compound tropicamide eye drops to dilate eyes, 3 - 5 drops/time, 10 minutes/time, and compress the lacrimal sac to avoid systemic absorption. After the pupils are completely dilated, assist the child in a reasonable position in the dark room, usually in a supine position. After fixing the head, give the baby a pacifier if necessary, and then give proparacaine hydrochloride eye drops into both eyes. Under topical anesthesia, the infant opened the eyelids with a lid opener, and a binocular indirect ophthalmoscope was followed by a +20D pre-scope and fundus exami-

nation using a scleral depressor. It should be noted that in the process of inspection, it is necessary to master the order, first, check the right eye, then check the left eye, first the optic disc, macula, posterior temporal, superior, inferior and nasal, and then inspect the retina in turn. In particular, the peripheral retina is examined. An experienced ophthalmologist was responsible for the screening of neonatal fundus diseases, and the screening results were recorded. During the examination, a neonatal monitor should be connected to closely monitor the neonatal heart rate, transcutaneous oxygen saturation, and other vital signs, to avoid fundus reflex-induced bradycardia, and excessive crying of the infant leading to suffocation, apnea, and other abnormal conditions happened. At the same time, the screening results are used as the basic basis to clarify the time of follow-up. If there are only stage I lesions or no lesions in both eyes, a follow-up examination will be carried out in the next 2 weeks until the retinal blood vessels grow to the serrated edge or ROP degenerates; for stage II lesions If the degree of ROP decreases during the follow-up period, the examination can be carried out every 2 weeks until the disease completely regresses; for children with stage III disease, 2 - 3 times a week re-examination, for lesions that reach the pre-threshold or threshold level, fundus laser photocoagulation or surgery should be performed as soon as possible.

4. Statistical Analysis

The data of this study were analyzed by SPSS 20.0 software, and the measurement data were expressed as mean ± standard deviation ($x \pm s$), a t-test was performed for comparison between groups, and the X^2 test for count data and the t-test for measurement data were performed according to the distribution characteristics of the data, the correlation analysis between ROP and a single risk factor was performed by chi-square test, while the correlation analysis between multiple risk factors and ROP was performed by Logistic regression analysis, with $P < 0.05$ indicating a statistically significant difference.

The basic principle of the logistic regression model:

$$\ln\frac{P}{1-P} = \mathrm{Logit}(\mathrm{P}) = \beta_{0+}\beta_1 \mathrm{x}_1 + \ldots + \beta_\mathrm{n}\mathrm{x}_\mathrm{n} + \varepsilon$$

The probability of a good patient ROP outcome is P (binomial categorical dependent variable $Y = 1$), and the probability of a poor outcome is $(1 - P)$ (binomial categorical dependent variable $Y = 0$). Logit transformation is performed on P, that is, P is transformed into an $[P/(1 - P)]$, which is recorded as Logit(P). The satisfaction probability prediction model can be obtained by the above transformation:

$$P = \frac{1}{1+\exp\left[-\left(\beta_0 + \beta_1 x_1 + \cdots \beta_{12} x_{12}\right)\right]}$$

Among them, P is the probability of the incidence of ROP; n is the total number of independent variables; β_1, β_2, …, β_n are the Logigistic regression correlation coefficients of each independent variable; X_1, X_2, …, X_n are the independent

variables that affect the incidence of ROP in patients.

5. Result

5.1. High Incidence of ROP in Preterm Infants of Pregnant Women with Gestational Diabetes Mellitus

Compared with the non-gestational diabetes group, the gestational diabetes group had a higher incidence of ROP, and the difference between the groups was statistically significant ($P < 0.05$), as shown in Table 1. This suggests that gestational diabetes may be an independent risk factor for ROP in premature infants.

5.2. Analysis of Clinical Data of Cases

We analyzed the relationship between gestational diabetes and gestational age and birth weight of preterm infants and found that the gestational diabetes group had slightly higher gestational age and birth weight compared with the non-gestational diabetes group, but the difference was not statistically significant ($P > 0.05$). In addition, there was no statistical significance in the age, gravidity, and parity of the two groups of pregnant women ($P > 0.05$), as shown in Table 2. It is suggested that the incidence of ROP in the gestational diabetes group may not be related to maternal age, gravidity, and parity, and has no significant effect on the gestational age and weight of preterm infants.

Table 1. Comparison of the incidence of ROP between the two groups.

Group	Number of examples	Number of ROP cases (n)	Incidence (%)
Gestational diabetes group	38	12	31.6
Non-gestational diabetes group	152	20	13.3
X^2 value			4.807
P value			0.028

Table 2. Comparison of clinical data between the two groups.

Project	Gestational diabetes group (n = 38)	Non-gestational diabetes group (n = 152)	t/x^2 value	P value
Gestational age				
<28 weeks	13 (34.21)	64 (42.11)	2.891	0.067
28 - 34 weeks	25 (65.79)	88 (57.89)		
Birth weight				
<1500 g	17 (44.74)	75 (49.34)	3.014	0.055
≥1500 g	21 (55.26)	77 (50.66)		
Age	31.55 ± 6.42	30.45 ± 5.12	1.192	0.237
Pregnancy (times)	2.79 ± 1.55	2.65 ± 1.26	0.602	0.548
Parity (times)	1.77 ± 0.67	1.67 ± 0.64	0.841	0.402

Table 3. Comparison of two groups by univariate analysis.

project	ROP group (n = 32)	Non-ROP group (n = 158)	X^2 value	*P* value
Gestational age				
<28 weeks	26 (81.25)	51 (32.28)	7.454	<0.001
28 - 34 weeks	6 (18.75)	107 (67.72)		
Gender				
Male	15 (46.87)	80 (50.63)	0.304	0.582
Female	17 (53.13)	78 (49.37)		
Birth weight				
<1500 g	24 (75.0)	52 (32.91)	18.386	<0.001
≥1500 g	8 (25.0)	106 (67.09)		
Bronchopulmonary dysplasia	19 (59.38)	28 (17.72)	15.386	0.001
Mechanical Ventilation	10 (31.25)	34 (21.52)	2.566	0.105
Maternal factors				
Age	27.18 ± 3.14	26.87 ± 3.72	0.744	0.451
fetal distress	21 (65.63)	117 (74.05)	6.263	0.011
Gestational hypertension	17 (53.13)	117 (74.05)	34.166	<0.001
Anemia	7 (21.88)	50 (31.65)	1.072	0.323
Blood transfusion	19 (59.38)	40 (25.32)	0.856	0.355
Mode of delivery				
Natural delivery	12 (37.5)	80 (50.63)	0.155	0.698
Cesarean section	20 (62.5)	78 (49.37)		
Oxygen usage				
Oxygen concentration > 50%	21 (65.62)	50 (31.65)	35.863	<0.001
Oxygen concentration ≤ 50%	11 (34.38)	108 (68.35)		

Table 4. Analysis of risk factors for ROP in premature infants.

Factor	Regression coefficients	standard error	WaldX2	*P value*	OR	95% CI
Gestational age	0.916	0.206	8.455	<0.001	2.487	1.671 - 3.732
Birth weight	0.888	0.317	9.186	<0.001	2.483	1.307 - 4.526
Oxygen usage	0.544	0.162	4.967	<0.05	1.778	1.284 - 2.436
Gestational hypertension	0.552	0.218	4.873	<0.05	1.735	1.123 - 2.655
Gestational diabetes	0.619	0.285	4.584	0.001	1.915	1.097 - 3.329
Fetal distress	0.712	0.335	3.156	0.019	2.035	1.055 - 3.915
Bronchopulmonary dysplasia	0.648	0.312	3.545	0.001	1.914	1.056 - 3.918

5.3. Univariate Analysis of the Incidence of ROP

Next, the effects of oxygen use, bronchopulmonary dysplasia, gestational hypertension, fetal distress, birth weight, and gestational age on ROP in preterm infants were further analyzed. Univariate analysis showed that there were significant differences in gestational age, birth weight, bronchopulmonary dysplasia, gestational hypertension, oxygen consumption of preterm infants, and fetal distress between the ROP group and the non-ROP group ($P < 0.05$), that is, the preterm infants in the ROP group had shorter gestational age, lower birth weight, and more patients with bronchopulmonary dysplasia; pregnant women with gestational hypertension, high concentrations of oxygen in preterm infants, and fetal distress had a higher incidence of ROP. Suggest that these may be risk factors for ROP. However, there were no significant differences in gender, mechanical ventilation, maternal age, and mode of delivery between the two groups ($P > 0.05$), as shown in **Table 3**.

5.4. Multivariate Analysis of the Incidence of ROP

Logistic multivariate analysis showed that gestational age, birth weight bronchopulmonary dysplasia, maternal hypertension, gestational diabetes, fetal distress, and oxygen consumption were associated with ROP, suggesting that these may be the main risks of ROP. Factors see **Table 4**.

6. Discuss

ROP is a retinal proliferative disorder that is characterized mainly by premature and low birth weight infants [8]. In recent years, with the continuous improvement of the treatment level of premature infants in the national neonatology department, the survival rate of premature infants has continued to improve, and the incidence of ROP has also shown an upward trend, which has become the main cause of blindness in children [9] [10]. Therefore, it is extremely important to explore the possible related risk factors for the occurrence of ROP, to achieve early detection and early intervention, and reduce the occurrence of blinding events [11] [12]. Therefore, by including the clinical data of 190 premature infants, this paper analyzes and explores the possible pathogenic factors of ROP and explores the ROP screening strategy suitable for this region. The results of this study are now discussed and analyzed.

6.1. Analysis of Risk Factors for the Incidence of ROP

In recent years, with the development of modern medical technology, the survival rate of premature infants has shown an obvious upward trend, but the incidence of ROP is increasing. By analyzing the epidemiological survey data, the incidence rates of ROP in Turkey and Beijing were 34.32% and 13.11%, respectively. Because each region has different screening standards, the incidence of ROP in different regions also has certain differences. Among the 190 premature infants in this study, 32 had ROP, with an incidence rate of 16.84%, slightly

higher than that in some regions at home and abroad. The reason may be related to the different screening standards adopted in each region [13]. For the pathogenesis of ROP, there are currently two clinically accepted theories, namely the oxygen free radical theory and the cellular molecular theory. ROP is a multifactorial disease, neonatal asphyxia, oxygen inhalation, birth weight, gestational age, cesarean section, multiple births, blood transfusion, anemia, bronchial dysplasia (BPD), application of pulmonary surfactant, neonatal Respiratory distress syndrome (NRDS), maternal gestational diabetes, gestational hypertension, cesarean section, vitamin E deficiency, use of certain antenatal drugs, corticosteroids, IVF, patent ductus arteriosus, convulsions, intracranial hemorrhage, Many factors, such as pulmonary hemorrhage and hyperbilirubinemia, are related to the occurrence and development of ROP. In normal fetuses, retinal vascularization begins at 16 weeks of embryonic life, vision occurs by 28 weeks, then the vitreous artery begins to degenerate, develops to the nasal Serrata by 36 weeks, and is fully vascularized until 40 weeks of gestation. There are many related factors involved in this process, including pigment epithelium-derived factor (PDF), placental growth factor (PIGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF2), among which the main function of FGF2 is Including the promotion of epidermal repair, tissue wound healing, stimulation of blood vessel formation, and promotion of fibroblast mesodermal cell mitosis and growth [14]. Studies have found that there is a clear correlation between the PI3K pathway and FGF2, and it has also been reported in the literature that retinal neovascularization (RNV) is inextricably linked to the PI3K signaling pathway [15]. Studies have found that FGF2, as a highly efficient growth factor, plays an extremely important role in the formation of pathological new blood vessels [16]. FGF2 will have a certain effect on the expression level of VEGF, promote the proliferation of vascular endothelial cells, and the proliferation of vascular endothelial cells has a synergistic effect with FGF2 and a hypoxic environment, and its effect is better than that of VEGF. Clinical research data show that the formation of retinal neovascularization is inextricably linked with the expression of VEGF. There are many types of factors in its family, including placental growth factor, VEGF-D, VEGF-C, VEGF-B, and VEGF-A. The formation of pathological blood vessels is related to VEGF-A, and the abnormal expression of vascular endothelial growth factor is also an important factor in the formation of retinal neovascularization. Some studies have found that the effect of PEDF on the retina is not limited to its maturation, development, and differentiation process. In the event of ischemic damage and mechanical damage to the retina, PDF also has neuronal protective effects. At present, the pathogenesis and risk factors of ROP are still unclear in clinical practice. Relevant kinds of literature point out that ROP has complex pathogenesis, and its risk factors include low gestational age and low birth weight of the fetus at birth. The same studies have found that fetuses with a gestational age of fewer than 28 weeks and a weight of less than 1500 g have a higher ROP stage and a relatively severe disease [17]. The reason

for this may be that the gestational age at birth is too small, the birth weight is lower than that of normal infants, and various functions of the body are not fully developed, especially the retinal development is immature, and premature infants themselves can lead to retinal damage. Due to the imperfect development of retinal blood vessels in premature infants, there are often avascular areas. Typically, intrauterine distress can induce hypoxia, and exposure to air after birth is located in a high-concentration environment because the retina is immature and highly sensitive to oxygen, which can promote retinal vasoconstriction, thereby presenting retinal hypoxia Status [18] [19]. Among perinatal women in my country, diabetes and hypertension are relatively common complications. The results of this study show that gestational hypertension and gestational diabetes are independent risk factors for the occurrence of ROP [20]. Consistent with research reports studies have shown that after the onset of gestational hypertension in patients with gestational hypertension, it can induce spasmodic contraction of the small arteries of the maternal body, increase the risk of thromboembolism in the placenta, and decrease the blood volume accordingly, further damage the placental function, and make the fetus unable to obtain enough. The lack of nutrients and oxygen hinders the normal growth and development of the fetus, thereby inducing the occurrence of intrauterine distress, low body weight, and premature fetal birth [21] [22] [23]. And others found in the literature report that after the onset of gestational diabetes mellitus, because the body is in a state of hyperglycemia for a long time, the risk of vascular lesions is increased, and the blood pressure level is further increased, which affects the fetal oxygen supply. This delays fetal growth and development. In this study, through univariate and multivariate Logistic regression analysis, it was found that oxygen consumption, gestational hypertension, gestational diabetes, fetal distress, bronchopulmonary dysplasia, birth weight, and gestational age were the main risk factors for ROP. The reasons for the analysis are as follows: 1) Maternal gestational diabetes. Diabetes, as a metabolic disease, is mainly characterized by chronic elevation of blood glucose level, which has a high incidence, and disturbance of glucose metabolism during pregnancy can affect maternal health and normal delivery of the fetus. It has been reported in the literature that the risk of preterm birth with gestational diabetes is 2.4 times higher than that of women without gestational diabetes [21] [24]. Some scholars analyzed the risk factors of ROP in their research and found that pregnant women with gestational diabetes mellitus are a more important risk factor, the main reason is that pregnant women with gestational diabetes can lead to the immaturity of fetal organs, especially gestational diabetes mellitus. It is the immature retina of premature infants that causes ROP. At the same time, abnormally elevated blood glucose levels in pregnant women can lead to an increased risk of preterm birth, and also have a direct impact on intrauterine growth and development of the fetus, especially fetal retinal development, so gestational diabetes is an independent risk factor for ROP; 2) maternal intrauterine infection. Studies have found that intrauterine infection in

the mother during pregnancy is likely to have a direct impact on the nutrient absorption of the placental tissue and interfere with retinal development. The retinal development of such fetuses after delivery is not high, resulting in retinopathy; 3) intrauterine fetal development distress. Most intrauterine distress occurs after labor, but some also occur during pregnancy, which is not only an important factor leading to neonatal neurological sequelae and perinatal fetal death but also ranks first in the cause of perinatal death. It has been reported in the literature that the occurrence of ROP is related to fetal distress, and it is believed that the reason may be related to the large span of changes in oxygen partial pressure from intrauterine anaerobic to sudden exposure to air [25]. At the same time, under normal circumstances, when the fetus is in respiratory distress, it can aggravate the hypoxia response of the body. This hypoxia response will have a direct impact on the development of the retina, affecting the developmental maturity of the retina, thereby increasing the risk of retinopathy; 4) neonatal complications. Compared with preterm infants without comorbidities, such as neonatal hyperbilirubinemia, neonatal pneumonia, respiratory distress, and apnea, the risk of retinopathy in preterm infants is higher. It is mainly related to neonatal complications such as neonatal hyperbilirubinemia, neonatal pneumonia, respiratory distress, suspension, etc., neonatal birth weight, and birth gestational age. Further analysis found that the higher the birth weight of premature infants. The lower and the younger the gestational age, the higher the risk of comorbidities, and the easier it is to develop retinopathy of prematurity; 5) oxygen use. In the occurrence and development of ROP, a high concentration of oxygen (oxygen concentration > 50%) is a more important factor. Because the lungs of preterm infants with low gestational age and low birth weight are immature and their lung function is imperfect, they often need oxygen support after birth. Oxygen is necessary to maintain life, but it is also a risk factor for premature infants. After delivery, premature infants directly enter the aerobic environment outside the uterus from the anaerobic environment in the uterus, and they are in a high-concentration aerobic environment form. Because the functions of various organs of newborns have not yet been fully developed, the antioxidant defense mechanism in their tissues cannot remove a large number of oxygen free radicals in time, damage the retinal tissue, promote vasoconstriction, make the retinal tissue in a state of hypoxia, and cause damage to the retinal neovascularization factors. Stimulation leads to the formation of new blood vessels in retinal tissue and induces the contraction of the neovascular membrane, thereby forming ROP [26]. At the same time, the study found that the fluctuation level of blood oxygen saturation is a more important factor in the occurrence and development of ROP. In the rat ROP model, both unstable and hypoxic oxygen environments are caused by ischemic retinopathy one main reason. Therefore, the occurrence of ROP is related to oxygen inhalation, and changes in the fluctuation range of blood oxygen saturation can lead to aggravation of the occurrence and development of ROP. It is stipulated in the "Guidelines for

the Treatment of Preterm Infants with Oxygen and Retinopathy Prevention and Control" that for children with percutaneous oxygen saturation < 85% or arterial oxygen partial pressure < 50 mmHg or combined with intrauterine distress, the target oxygen level percutaneous. The blood oxygen saturation is 90% - 95%, and the arterial oxygen partial pressure is 50 - 80 mmHg. At the same time, the retinal development of premature infants stops after birth, because the retina is not yet mature, and its blood vessels are highly sensitive to oxygen. If oxygen inhalation is supplemented for a long time, the partial pressure of choroidal oxygen in premature infants can continue to increase and induce retinal vascular occlusion, contraction, the occurrence of this situation will greatly reduce the oxygen content of the choroidal blood vessels, so that the retina has a hypoxic response, stimulate the formation of new blood vessels, and lead to retinopathy; 6) birth weight. Birth weight is a clinically recognized risk factor in the occurrence and development of ROP. Generally speaking, the birth weight of the newborn is often proportional to the gestational age, that is, the smaller the gestational age of the newborn, the lower the birth weight, the less perfect the retinal development is, and the more prone to retinopathy; 7) age. Existing studies have shown that the development of the temporal retinal vessels of the fetus is inseparable from the support of the outer layer of cells and the matrix. This development can only be completed when the fetus is full-term. The younger the age, the less the outer layer of cells and matrix support, and the lower the maturity of the temporal retinal vascular development. At the same time, the immature retinal blood vessels will shrink violently, resulting in vascular atresia and blood interruption, so that new blood vessels appear on the retina, resulting in retinal proliferative lesions [27]. This study found that the occurrence of ROP has nothing to do with the mode of delivery, and there is currently no consensus on the relationship between ROP and the mode of delivery [28]. Some scholars have found in related studies that the risk of neonatal retinal hemorrhage is related to the mode of delivery. Compared with cesarean section, vaginal delivery can increase the risk of retinal hemorrhage, and vaginal delivery is an independent risk factor for ROP [29], this study also has certain limitations. At present, both international and domestic advocate vaginal delivery, and the sample size of this study is relatively limited. If the sample content is further expanded, the result may not be the same and other studies found that the occurrence of ROP requiring treatment is related to natural childbirth [30]. However, some other studies reported in the literature that there is no clear relationship between the mode of delivery and the occurrence of ROP [31]. Therefore, whether there is a correlation between the occurrence of ROP and the mode of delivery needs to be further expanded in the sample data, or further confirmed by multi-center studies.

6.2. Screening Strategies for ROP

Although ROP is an important factor leading to blindness in children, the only

way currently found to prevent the development of lesions is timely screening, finding problems, and taking effective treatment measures as soon as possible, which will ultimately help children get a good prognosis, reduce the incidence of blindness, improve the long-term quality of life of children, improve the family happiness index, and reduce the burden on families and society. A study found that large-scale screening can reduce the missed diagnosis rate of children with ROP, but expanding the scope of screening objects will cause waste of medical resources on the one hand, and increase the suffering of children on the other hand [32]. Therefore, it is particularly important to develop a screening standard that is consistent with the characteristics of the NICU. Regarding the screening standards for ROP, there are certain differences in different countries and regions. For example, in the United Kingdom, the gestational age is <31 weeks or the birth weight is <1500 g; in the United States is the gestational week < 28 weeks or the birth weight < 1500 g; other European countries for example, in Sweden, the Netherlands, France, and Germany, the screening criteria are gestational age < 32 weeks or birth weight < 1500 g [33]. The Beijing Retinopathy of Prematurity Epidemiological Investigation Team suggested that local NICUs should use their observations as the basic basis to formulate screening standards that are consistent with their NICU characteristics. In this region, better cost-efficiency results can be obtained if screening is narrowed to <32 weeks gestational age or birth weight < 1500 g. It should be noted that the screening standards of a region and country are based on the local ROP detection rate, which needs to be formulated in combination with risk factors, for example, for gestational age < 34 weeks or birth weight < 2000 g. Newborns, if they have a history of oxygen inhalation, ventilator-assisted breathing, blood transfusion, etc., should expand the scope of screening accordingly. With the increase in the birth rate of premature infants and the detection rate of ROP, coupled with the improvement of the NICU monitoring level, we need to adjust the screening standards to adapt to the new situation in a certain period and use the epidemiological data of different regions as based on the basic basis, it is feasible to formulate screening standards that meet the local area. There are certain differences in the understanding of the screening purpose and occurrence mechanism of ROP in different countries in the world, so the time of initial screening for ROP is also different. The time of initial screening for ROP has always been controversial. Western countries generally use postnatal age (PNA) as a single criterion to determine the initial screening time for ROP, that is, the initial screening at 4 weeks after birth; while the United States uses a double standard of corrected gestational age and postnatal age [34]. In recent years, by analyzing the risk factors for the occurrence of ROP, in some studies, some scholars suggested that the age of the child should be based on the week after birth. The main reason is that the gestational age is calculated based on the last menstrual period (LMP). Or if the pregnant woman has an incorrect memory of LMP, the incorrect corrected gestational age or corrected gestational age will be calculated, which will affect the time of the

initial ROP screening, resulting in missed diagnosis or misdiagnosis. Therefore, the use of postnatal age as the standard is relatively reliable. A multicenter study from CRYO-ROP reported that corrected gestational age or corrected gestational age was associated with threshold ROP lesions and ROP, so the gestational age or weight of children at birth was not related to corrected gestational age or corrected gestational age. Some scholars believe that the corrected gestational age or corrected gestational age should be used as the main criterion when calculating the initial screening time of ROP. Some regions and countries also believe that it is more convenient to use the corrected gestational age or the corrected gestational age standard, mainly because it is not easily affected by the gestational age or weight of the child. For determining the time of the initial screening, this study advocates that the corrected gestational age and postnatal age should be fully considered, and the earlier of the two should be selected, which should be combined with the clinical risk factors such as blood transfusion, oxygen inhalation, and mechanical ventilation, to define an appropriate initial screening and re-screening time, to detect pre-threshold lesions in time, and take effective intervention measures as soon as possible, to control the progression of the disease and reduce the occurrence of malignant events such as blindness. In 2015, a multi-center study in my country [35] suggested the following follow-up plan: 1) No ROP or ROP1 lesions: follow-up every other week until the gestational age was corrected at 44 weeks or the lesions regressed and disappeared. 2) ROP2 lesions: follow up once a week until the gestational age is corrected at 44 weeks or the lesions regress and disappear. 3) Lesions before the threshold: follow up once a week, consider laser or cryotherapy. 4) Lesions with the threshold of ROP3: it is recommended to contact the local hospital for emergency laser or cryotherapy within 72 hours. 5) ROP4 stage lesions: scleral cerclage or vitrectomy is recommended. 6) ROP stage 5 lesions: vitrectomy is recommended. When determining the principle of follow-up for ROP, it is often not related to the risk factors and incidence of ROP. It is mainly based on the ET-ROP and CRYO-treatment guidelines and the international classification of ICROP. Currently, countries around the world have the same principle of follow-up. The screening results were used as the basic basis to determine the follow-up interval. In the United States, for zone 1 and 2 lesions, follow-up is conducted weekly; for incomplete vascularization in zone 1 and 2, it is conducted every 2 weeks; and for incomplete vascularization in zone 2, it is conducted every 2 - 3 weeks follow-up. The current principle in my country is that if the disease is below the threshold, follow-up is performed every 2 weeks; if the pre-threshold disease category 2 or omental vascularization is limited to zone I, follow-up is performed once a week. Although there are some differences in the expressions in different countries in the world, they have the same standard, among which the United States has complete retinal vascularization in zone 3, while my country has complete omental vascularization. At the same time, the Anglo-American joint multi-center study proposed three indications for discontinuing follow-up for ROP, as follows: 1)

complete retinal vascularization; 2) retinal vessels grow into zone 3 without zone 2 ROP lesions; 3) corrected fetal at the age of 45 W, there is no progression or no pre threshold disease [36]. During the screening, if one of the above three indications occurs, screening is stopped.

6.3. Fundus Lesions and Treatment of ROP

ROP lesions are mainly divided into 5 stages, pre-threshold lesions, rapidly progressive ROP, and regressive stages. The guidelines propose that during the ROP screening process, follow-up can be continued for stage I and stage II lesions. Once stage III lesions are found, treatment should be started in time. At present, the main international surgical treatment options are laser photocoagulation therapy, condensation therapy, and intravitreal injection of Arizona monoclonal antibody. In this group of data, the fundus lesions of the 32 ROP premature infants were mainly concentrated in stage III/III+, a total of 13 cases, accounting for 40.6%, and 3 cases with a pre-threshold disease, accounting for 9.4%. The intravitreal injection of ranibizumab alone was performed. 2 cases were treated with laser photocoagulation alone, 2 cases were treated with laser photocoagulation alone, and 1 case was treated with intravitreal injection of ranibizumab combined with laser photocoagulation. The choice of retinopathy surgery is also debated in China [36]. compared the efficacy of intravitreal injection of ranibizumab and laser therapy in type I and threshold retinopathy of prematurity through Mata analysis, indicating that laser therapy May be more effective than an intravitreal injection of ranibizumab. In addition, some scholars believe that laser treatment of ROP has a high success rate and significantly reduces the number of operations. It should still be the first choice for ROP treatment [37]. However, compared with laser photocoagulation surgery, intravitreal drug injection has fewer complications, the peripheral retinal damage is mild, and the long-term efficacy of laser surgery has not been accurately reported. Due to the small sample size of this group of data, the difference and efficacy of the two surgical methods cannot be compared, and further clinical research is needed for the selection of surgical methods.

7. Conclusions

1) Gestational diabetes may be one of the independent high-risk factors for ROP. So it is particularly important to take effective measures to control maternal blood glucose levels during pregnancy.

2) Many factors such as gestational age, birth weight, and oxygen intake of premature infants are related to the occurrence and development of ROP, that is, the smaller the gestational age, the lower the birth weight, and the longer the oxygen therapy time and the higher the concentration, the higher the incidence of ROP high. We should pay attention to health care during pregnancy, strengthen health education, and reduce the incidence of premature delivery, to prevent ROP.

3) When determining the initial screening time of ROP, the double standard of postnatal age/corrected gestational age should be used, and the earlier of the two should be selected, especially the preterm infants with gestational diabetes mellitus as the key screening object.

Acknowledgements

In all humility I bow before Allah, the compassionate and the most Merciful who bestowed us with heart to feel and brain to think, so that we know what we do not.

All respect and praise to the Holy Prophet (P.B.U.H) and his Ahl al-Bayt (A.S), who came as a light of knowledge for all seekers and a real role model for all mankind.

I am very thankful to my senior Dr. Yongfeng Zhang General chief director of pediatric Department of The Affiliated Hospital of Weifang Medical University, China for his patience, inspiring guidance, kind attitude and cooperation throughout my research work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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