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RETINOPATHY OF PREMATURITY AND MATERNAL AGE

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Abstract

Purpose—To determine the risk factors, especially maternal risk factors, associated with the development of retinopathy of prematurity (ROP) in premature babies.

Methods—A matched case–control study involving premature patients was undertaken retrospectively. The case group consisted of premature babies with the subsequent development of ROP. The control group consisted of gestational age-matched and sex-matched premature babies that did not develop ROP during the follow-up period. Risk factors involving patient demographics and maternal characteristics were compared between the case and control groups.

Results—A total of 144 patients were included in this study (72 patients in the case group and 72 patients in the control group). Among the 66 possible risk factors compared, only birth weight and maternal age were found to be significant risk factors. Birth weight was significantly lower in the case group ($1,248.7 \pm 257.8$ g vs. $1,335.5 \pm 297.2$ g, $P = 0.01$), and maternal age was significantly older in the case group compared with that in the control group (31.2 ± 5.1 years vs. 28.2 ± 5.3 years, $P < 0.001$). The odds ratio of having babies with ROP was 2.9 when the maternal age was >30 years.

Conclusion—Older maternal age is a newly identified risk factor for the development of ROP in premature babies.

Keywords

maternal age; retinopathy of prematurity; risk factors

Retinopathy of prematurity (ROP) remains a major cause of childhood blindness despite improvements in neonatal intensive care and survival throughout the world. Previously identified risk factors associated with ROP include low birth weight, young gestational age, nonblack race, multiple births, birth outside of a study center, prolonged elevation of arterial oxygen levels, hypoxemia, hypercarbia, respiratory distress syndrome, apnea, erythrocyte transfusions, sepsis, intraventricular hemorrhage, prolonged parenteral nutrition, methylxanthine administration, treatment with indomethacin, renal insufficiency, and poor postnatal weight gain.^{1–14} Maternal risk factors such as body mass index, first partum, delivery (vaginal delivery or cesarean section), in vitro fertilization, premature rupture of membranes, placental abruption, and preeclampsia, are less frequently explored.^{15–17} The aim of this study was to identify the risk factors, mainly maternal risk factors, associated with ROP in a Taiwanese population.

Materials and Methods

The study was approved by the Institutional Review Board at Chang Gung Memorial Hospital, Taoyuan, Taiwan. A matched case-control study was undertaken retrospectively at Chang Gung Memorial Hospital from 2002 to 2004. The case group consisted of cases of premature babies that subsequently developed ROP. The control group consisted of 72 gestational age-matched and sex-matched premature babies that did not develop ROP during the follow-up period. A gestational age of <37 weeks was considered to be premature. The data of patients' characteristics, presence of systemic disorders, medications and treatments, and maternal characteristics were collected (Table 1).

Data were studied using SAS 9.0 software (SAS Institute, Inc., Cary, NC). McNemar's test or a paired *t*-test was conducted to compare the demographic data between the two groups. We also conducted conditional logistic regression to explore the risk factors of ROP. Finally, the chi-square test for independence was conducted to examine whether the significant risk factors were dependent on each other. A *P* value <0.05 was considered significant.

Results

There were 1,074 premature babies screened at our hospital during the time period of the study. Of these, there were 938 premature babies that did not develop ROP and 136 babies with ROP detected during this period. Matching for this case-control study was completed with 72 case-control matched pairs. In total, 144 patients consisting of 72 premature babies with varying degrees of ROP and 72 premature babies without ROP were included in this study. Among the 72 patients in the case group, 40 patients (56%) had Stage 1 ROP, 18 patients (25%) had Stage 2 ROP, 13 patients (18%) had Stage 3 ROP, and 1 patient (1%) had Stage 4 ROP. None of the patients developed Stage 5 ROP. Concerning the zone of ROP, 1 patient (1%) had Zone 1 ROP, 45 patients (63%) had Zone 2 ROP, and 26 patients (36%) had Zone 3 ROP. Eleven patients (15%) received laser treatment for prethreshold or threshold ROP, and 1 patient (1%) received scleral buckling for the treatment of retinal detachment. The average gestational age for the case and control groups was 29.1 ± 1.7 weeks. The basic characteristics of these patients are listed in Table 2.

Among the 66 possible risk factors compared, only birth body weight and maternal age were found to be significant risk factors. Birth weight was significantly lower in the case group ($1,248.7 \pm 257.8$ g vs. $1,335.5 \pm 297.2$ g, $P = 0.01$). To further analyze the risk factor of birth weight, we classified their weights into 3 groups: Group 1 (birth weight <1,156 g, $n = 47$); Group 2 (birth weight between 1,156 g and 1,390 g, $n = 49$); and Group 3 (birth weight >1,390 g, $n = 48$). When compared with Group 3 (odds ratio = 1), the odds ratios of having ROP was 3.7 and 2.0 for Groups 1 and 2, respectively. Maternal age was significantly older in the case group than that in the control group (31.2 ± 5.1 years vs. 28.2 ± 5.3 years, $P < 0.001$). The odds ratio of having ROP babies was 2.9 when the maternal age was >30 years (95% confidence interval: 1.4 to 6.2; Table 3). The chi-square test for independence of these 2 factors was nonsignificant ($P = 0.09$), indicating that these 2 factors were independent risk factors for ROP.

Discussion

In this gestational age-matched and sex-matched case-control study, performed in a tertiary medical center on Taiwanese premature babies born at <37 weeks of gestation, we set out to determine the risk factors, particularly the maternal risk factors, associated with the development of ROP in the moderately industrialized country of Taiwan. From 2002 to 2004, the data from our neonatal intensive care unit show that the incidence of ROP was 13% (136 of 1,074). After matching for gestational age in both the case and control groups, 66 possible

risk factors were analyzed. The two significant risk factors identified from the data were low birth weight and advanced maternal age. In the case group, the birth body weight was significantly lower ($1,248.7 \pm 257.8$ g vs. $1,335.5 \pm 297.2$ g, $P = 0.01$) and maternal age was significantly higher (31.2 ± 5.1 years vs. 28.2 ± 5.3 years, $P < 0.001$) when compared with the matched control group. The odds ratio of having babies with ROP was 2.9 when the maternal age is over 30.

In our study, low birth weight is a well-known risk factor,^{1,2,5–8,11–16} and increased maternal age is a newly identified risk factor for the development of ROP. In the last few decades in Taiwan, the average age of marriage continues to increase, resulting in increased maternal age at childbirth. In 2007, the average age of marriage for women in Taiwan was 29.2 years compared with the average age of 28.7 years in 1997, 26.1 years in 1987, and 24.0 years in 1977 (Department of Households, Ministry of Interior, Taiwan). This might be one of the reasons why advanced maternal age was not an issue in the past and this risk factor was not identified in previous studies. As is the case with Western developed nations, increased maternal age in our study group may be attributed to women deciding to pursue their education and career goals, resulting in marriage and childbirth at a relatively later time in their lives compared with women a few decades ago.¹⁸ Increased maternal age is associated with many other conditions, including Down syndrome,¹⁹ Turner syndrome,²⁰ autism spectrum disorders,²¹ defects in cardiac septation,²² cystic fibrosis, and hemoglobinopathies.²³ Drazdiene et al.²⁴ performed a retrospective analysis of ROP risk factors in 256 premature infants. In their study, they found a trend of increased maternal age and the development of ROP. The maternal age for premature infants without ROP, infants with ROP without the need for surgery, and infants with ROP and the need for surgical interventions was 27 ± 7 years, 28 ± 9 years, and 30 ± 6 years, respectively. The P value did not reach statistical significance, which may be related to the smaller case numbers analyzed. However, their findings regarding the association between advanced maternal age and the risk of treatment-requiring ROP are similar to our results and are of clinical importance. Although the exact etiology of increased maternal age in relation to the development of ROP is still unclear, it is well known that increased maternal age contributes to chromosomal abnormalities, hypertensive complications, miscarriage, stillbirth, and declining fertility.²⁵

A later age of conception increases the likelihood of giving birth to children who have conditions associated with chromosomal abnormalities and alterations.²⁶ The primary risk factors identified for errors occurring in oocytes, where nondisjunction of chromosome occurs, are maternal age and altered recombination.¹⁹ The maternal effect may also be associated with the increased risk of malsegregation of oocytes, a recombinant-independent factor, because of environmental-related and age-related insults accumulating in the ovaries as a woman ages.²⁷ Oocytes from older women may be predisposed to becoming aneuploid as a consequence of an age-long decline in the cohesive ties holding chromosomes together and a declining ability to respond and block division during meiosis Phase I.^{28,29} Another mechanism of aberrant chromosomal alteration that increases with advanced maternal age is related to the maternal polymorphisms of the homocysteine/folate pathway.³⁰ Advanced maternal age is also well characterized with elevated gonadotropin levels because of decreased ovarian reserve; such high levels of gonadotropins are also seen to increase the risk for having a baby with a chromosomal abnormality.³¹ During the normal aging process, the age-dependent decline in capability and capacity to dispose of oxyradicals results in increased sequence alterations and mutations.³²

Retinopathy of prematurity has been linked to certain gene defects such as Norrie disease (NDP) gene³³ and frizzled-4 (Fz4) gene.³⁴ The Norrin-Fz4 signaling system plays a central role in vascular development in the retina.³⁵ The NDP gene sequence alterations have been reported in 11% of affected patients with severe ROP in an ethnically diverse group of

premature infants.³⁶ Retinopathy of prematurity is also found to be associated with the polymorphism of vascular endothelial growth factor, which is the principle growth factor for the development of neovascularization in advanced ROP.³⁷ Increased maternal age, as a function of age, time, and continuous exposure of genetic elements to the matrix that contains great amounts of reactive oxygen species and free radicals, could play a significant contributing role in gene sequence alteration and development of ROP.³⁸ However, whether increased maternal age directly increases the likelihood of these signaling defects or whether there is another signaling pathway related to ROP remains unknown and requires further investigation.

Our results from the matched case-control subjects show that low birth weight and increased maternal age are significant risk factors associated with the development of ROP. However, we failed to find previously identified risk factors such as preeclampsia,¹⁶ intraventricular hemorrhage,^{1,14,17} necrotizing enterocolitis,¹⁶ and bronchopulmonary dysplasia^{1,6} to be significant risk factors. It is possible that in comparing studies conducted on different patient populations, race, and ethnicity, selectivity could result in these different findings. It is also possible that these previously identified risk factors may be minor risk factors rather than major risk factors in the pathogenesis of ROP, which results in different studies showing inconsistent conclusions regarding the same risk factor.^{1,6}

Our study is limited by its retrospective nature and small sample size. Further studies using large, population-based cohorts with precise assessments of exposures and potential confounders are needed. Increased maternal age seems to be a newly identified risk factor associated with ROP, and this continuing trend of conception at a later age calls for more attention to this increasingly important issue. From a clinical standpoint, we can use this newly identified risk factor to screen and identify possible cases of ROP while counseling expectant mothers of increased maternal age.

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Table 1**Risk Factors Compared Between Case and Control Groups**

Categories	Variables
Patients' characteristics	Sex, birth body weight, gestational age, Apgar score, and duration of ventilation therapy
Presence of systemic disorders	Anemia, bronchopulmonary dysplasia, apnea, hyperbilirubinemia, cerebral palsy, intraventricular hemorrhage, necrotizing enterocolitis, pneumonia, sepsis, patent ductus arteriosus, atrial septal defect, ventricular septal defect, respiratory distress syndrome, and other diseases
Medications and treatments	Aminoglycosides, other antibiotics, transfusion, corticosteroid, dopamine, phototherapy, furosemide, indomethacin, intralipid infusions, surfactant, vitamin E, xanthine derivatives, benzodiazepines, operations, and others medications
Maternal characteristics	Nationality (Taiwanese/non-Taiwanese), occupation, education, age, body mass index, parity, delivery type, in vitro fertilization, premature rupture of membranes, placental abruption, bleeding, twin or multiple births, history of abortion, smoking, alcoholism, betel nut consumption, hypertension, diabetes mellitus, hepatitis infection, epilepsy, preeclampsia, gestational diabetes mellitus, pregnancy-induced hypertension, other diseases, conception drug use, steroid use, insulin use, antiepileptic drugs use, β -blocker use, other antihypertensive drug use, magnesium sulfate, and other drug use

Table 2

Demographics of the Case and Control Groups

Variables	Case (n = 72)	Control (n = 72)	P
Mother			
Age (years), mean (SD)	31.2 (5.1)	28.2 (5.3)	0.0002*
Infant			
Gestational age (weeks), mean (SD)	29.1 (1.7)	29.1 (1.7)	0.3*
Body weight (g), mean (SD)	1,248.7 (257.8)	1,335.5 (297.2)	0.01*
Gender, n (%)			
Male	38 (52.8)	38 (52.8)	0.6 [†]
Female	34 (47.2)	34 (47.2)	
Apgar score, mean (SD)	7.4 (1.7)	7.6 (1.4)	0.5*
Associated with other diseases, n (%)			
Yes	8 (11.1)	16 (22.2)	0.1 [†]
No	64 (88.9)	56 (77.8)	

* By paired *t*-test.

[†] By McNemar's test.

SD, standard deviation.

Table 3

The Odds Ratio of ROP With Different Birth Weight and Maternal Age

Variables	ROP	No ROP	Odds Ratio [*]	95% CI	P
Birth weight (g)					
<1,156	28	19	3.7	(1.1–12.9)	0.04
1156–1,390	24	25	2.0	(0.7–5.6)	0.2
>1,390	20	28	— [†]	—	—
Mother's age (years)					
>30	37	18	2.9	(1.4–6.2)	0.005
≤30	35	54	—	—	—

^{*} Odds ratio was performed by conditional logistic regression.

[†] Dashes indicate reference groups.

CI, confidence interval.