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# Retinopathy of prematurity in Saudi Arabia: Exploring maternal risk factors

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## Abstract:

**PURPOSE:** Retinopathy of prematurity (ROP) is a preventable blinding disorder affecting preterm infants. To date, maternal risk factors have not been studied in Saudi Arabia. This study aims to identify possible maternal risk factors for any stage and type 1 ROP.

**MATERIALS AND METHODS:** A total of 295 preterm infants screened for ROP between November 2013 and December 2018 at a Saudi Arabian tertiary-care hospital were included. We included infants with a gestational age  $\leq 32$  weeks and/or birth weight (BW)  $\leq 1500$  g. We analyzed 28 maternal and neonatal risk factors.

**RESULTS:** The incidence of ROP at any stage and Type 1 were 31.9% and 7%, respectively. In the univariate analysis, the only maternal factor associated with any stage of ROP was spontaneous vaginal delivery ( $P = 0.049$ ), but no maternal factor was an independent risk factor for type 1 ROP. Multivariate logistic regression analysis identified lower BW, lower gestational age and longer neonatal intensive care unit stay as independent risk factors for the development of ROP at any stage ( $P < 0.05$ ). For Type 1 ROP, lower BW, and intraventricular hemorrhage were significant independent risk factors ( $P < 0.05$ ).

**CONCLUSION:** The only maternal risk factor related to ROP was spontaneous vaginal delivery, which increased the risk of any stage of ROP. The single most predictive risk factor for any stage of ROP and Type 1 ROP was low BW. These findings emphasize the role of the obstetrician in promoting health care and modifying maternal risk factors to prevent preterm births related to a low BW.

## Keywords:

Birth weight, maternal, neonatal, retinopathy of prematurity, risk factor

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## Introduction

Retinopathy of prematurity (ROP) is a disease in premature infants affecting the development of retinal blood vessels and can lead to blindness early in life.<sup>[1]</sup> ROP has been described as the second most frequent morbidity in a Saudi Arabian neonatal intensive care unit (NICU), only exceeded by respiratory distress syndrome (RDS).<sup>[2]</sup> The incidence of ROP in Saudi Arabia has been reported to range from 23% to 56%.<sup>[2-6]</sup>

To better manage ROP, we need to study the disease as an event affected by various factors occurring before pregnancy, during pregnancy, and after birth.<sup>[7-9]</sup> Many studies have identified neonatal risk factors including low gestational age (GA), low birth weight (BW), prolonged oxygen exposure, sepsis, interventricular hemorrhage, and blood transfusions are associated with ROP.<sup>[10-12]</sup> However, the relationship of other, especially maternal, risk factors has not been extensively examined,<sup>[13]</sup> no Saudi Arabian studies have evaluated maternal risk factors.<sup>[2,3,6]</sup>

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Studies have revealed an association of ROP with maternal age,<sup>[14]</sup> smoking,<sup>[15]</sup> mode of delivery,<sup>[16,17]</sup> and diabetes.<sup>[18]</sup> Preeclampsia plays a controversial role in ROP; while some studies reported an inverse relationship with ROP,<sup>[19]</sup> others observed an increased risk of ROP.<sup>[20]</sup> Specifically, maternal conditions associated with defects in placental circulation causing fetal hypoxia have raised interest. Results of a large study showed higher ROP incidences among infants whose mothers had the following complications during pregnancy: Heavy cigarette smoking, second or third trimester bleeding, severe diabetes or anemia, moderate-to-severe preeclampsia and ruptured fetal membranes with or without infection.<sup>[15]</sup>

In this report, we studied a series of suspected maternal and neonatal risk factors for ROP to identify independent risk factors linked to the development of any stage or Type 1 ROP that require treatment. To the best of our knowledge, this is the first study to explore maternal risk factors in a Saudi population of preterm infants.

## Materials and Methods

### Research subjects

This retrospective cohort study was conducted at the NICU of a Saudi tertiary university hospital. Data were collected from medical records of patients admitted to the NICU between November 2013 and December 2018. We included all infants with a GA  $\leq$  32 weeks and/or BW  $\leq$  1500 g who were screened for ROP. Eligible infants who did not complete all screening sessions and/or did not have a recorded final ROP examination were excluded. The study was approved by the Institute's Biomedical Ethics Research Committee (Reference No 156-15). Informed consent from the guardians was waived due to the retrospective nature of the study. The study has been conducted in accordance with the World Medical Associations' Declaration of Helsinki.

### The data collection included

#### Demographics

GA, BW, plurality (singleton or multiple), sex, and nationality.

#### Antenatal maternal risk factors

1. Hypertensive diseases of pregnancy: Chronic hypertension, preeclampsia, and eclampsia
2. Diabetes: Chronic and gestational diabetes
3. Pregnancy-related factors: Preterm premature rupture of membranes (PPROM), antenatal steroids (ANS), mode of delivery (Cesarean section [CS], spontaneous vaginal delivery [SVD]).

#### Neonatal risk factors

- a. Birth data and course of admission: Apgar score at 1 and 5 min, resuscitation at birth, poor weight gain at 6 weeks and length of stay in the NICU

- b. Neonatal comorbidities and interventions: Anemia, RDS, bronchopulmonary dysplasia (BPD), patent ductus arteriosus, intraventricular hemorrhage (IVH), hyperglycemia, oxygen therapy, surfactant therapy, blood transfusion, and insulin therapy.

### Retinopathy of prematurity screening criteria

Screening criteria were based on the (2013) American Academy of Pediatrics policy.<sup>[21]</sup> The first examination was performed at 4 weeks postdelivery or at a corrected GA of 31 weeks, whichever was later. The infants were followed up weekly or biweekly until full vascularization of zone 3 or ROP regression was confirmed. Patients needed treatment if they met the early treatment for ROP (ETROP) definition of type 1 ROP.<sup>[22]</sup> Treatment with diode laser or anti-vascular endothelial growth factor (anti-VEGF; bevacizumab 0.675 mg/0.03 mL) followed the guidelines of the ETROP and bevacizumab eliminates the angiogenic threat of ROP (BEAT-ROP) studies.<sup>[22,23]</sup> All findings and interventions were documented for each eye following the standardized documentation of the revised International Classification of ROP,<sup>[24]</sup> including the zone (1–3), the stage (1–5), presence or absence and extent of the disease in clock hours.

The examination was performed by a pediatric ophthalmologist or a retina specialist experienced in ROP screening. Dilatation was initiated 1 h before the examination with cyclopentolate 0.25% and phenylephrine 2.5%, instilled three times every 10 min. A topical anesthetic was applied and a sterile pediatric speculum was used to open the eye. An indirect ophthalmoscope and a 28 diopter (D) lens were used with a sterile scleral depressor to examine the periphery of the fundus until the ora serrata was seen, the anterior border of the retinal vascularization was identified, or retinopathy was confirmed.

### Statistical analysis

Data analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) Version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were checked for normality using the Shapiro–Wilk test. Results were expressed as mean  $\pm$  standard deviation for normally distributed data, median (interquartile range) for non normally distributed data and frequencies (proportions) for categorical variables. Student's *t*-test was used to compare the means of continuous variables among those who developed ROP and those who did not.

Multivariate logistic regression analysis was used to identify predictors of ROP. Initially, a correlation matrix was created to check for high collinearity in any independent variables using Pearson's or Spearman's correlation tests according to the variable type and distribution. Univariate logistic regression was used

to examine the association of each potential predictor with the outcome variable (any stage ROP). Neonatal and maternal independent variables that were highly correlated were included in a multivariate logistic regression analysis (backward selection). The same process was performed when assessing possible related risk factors for the variable "type 1 ROP." The final model included the significant neonatal and maternal predictors in addition to the well-known predictors of ROP (BW and GA). A subanalysis was performed to identify any difference between risk factors of infants born vaginally and those born by CS. The model fit was tested using Hosmer–Lemeshow goodness of fit statistic. Odds ratio (ORs) and 95% confidence intervals (CIs) for each predictor were reported. A  $P < 0.05$  was considered statistically significant.

## Results

In our study, 295 infants were screened, of which 94 (31.9%) had ROP of any stage in at least one eye during at least one examination and 21 (7%) was of type 1 ROP. Table 1 compares the incidence of ROP in our study with those in other studies conducted in different regions of Saudi Arabia. The majority of patients in our study had stage 1 ROP (66%), whereas 23%, 10% and 1% had stage 2, 3, and 4, respectively. Of the ROP-positive patients, only 21 (22%) required treatment in both or either eyes. The most frequent treatment was by laser in 14 patients (67%), both laser and anti-VEGF treatment with bevacizumab were needed in 4 patients (19%), bevacizumab alone was needed in 2 infants (10%) and surgical intervention in 1 (5%). The median time from birth to the initial detection of ROP was 40 days (range 24–177 days) and time to treatment was 72 days (range 39–179 days). After treatment, no recurrence was observed.

### Demographics

Of the 295 infants enrolled in the study, 195 (66%) were from multiple birth pregnancy. Our data included 148 (51%) Saudi patients and almost equal numbers of males and females. The mean GA of the overall study group was  $28.0 \pm 2.4$  weeks, and the mean BW was  $1086.8 \pm 266.6$  g. Table 2 presents the characteristics

among the three groups: No ROP, nontreated ROP and treated ROP group. None of the treated infants had a GA  $> 30$  weeks (median, 28 weeks; range, 23–30 weeks) or a BW  $> 1000$  g (mean, 767.8 g; range, 527–1000 g).

### Maternal risk factors

Only one maternal risk factor, i.e., SVD, increased the risk of any stage ROP in the univariate analysis (OR = 0.598, 95% CI 0.358–0.998,  $P = 0.049$ ). No other maternal risk factors were identified [Table 3]. With regards to indicators of hypoxia such as Apgar scores at 5 min, the need for oxygenation and resuscitation at birth, both SVD and CS groups had similar outcomes. In addition, vaginally delivered neonates did not have more comorbidities such as RDS, sepsis, and/or IVH. However, vaginally delivered neonates were found to have statistically significant lower GA (mean  $28.2 \pm 2.2$ ) when compared to our CS (mean  $29.2 \pm 2.5$ ) ( $P = 0.001$ ).

### Neonatal risk factors

The following factors were considered independent predictors for any stage ROP in the multivariate analysis: Lower BW, lower GA, and longer stay in the NICU [all  $P < 0.05$ ; Table 4].

In the multivariate analysis of type 1, ROP BW and IVH were identified as significant independent risk factors [all  $P < 0.05$ ; Table 5].

BW was the best predictor for both any stage ROP and type 1 ROP [Tables 4 and 5]. In the group of extremely preterm infants (GA  $< 28$  weeks), there was a 7.0-fold increase in the risk of any stage ROP with each decrease in GA by 1 week (OR = 7.040, 95% CI 3.933–12.601,  $P < 0.001$ ). In the same group, the risk of treatment was increased by 3.2-fold with each decrease in GA by 1 week (OR = 3.203, 95% CI 1.117–9.186,  $P = 0.026$ ). In that group, the ROP incidence was 50%, and 71.4% of the affected infants needed ROP treatment.

## Discussion

This study aimed to expand our knowledge on the risk factors for developing ROP in Saudi Arabia. In agreement

**Table 1: Incidence of retinopathy of prematurity in the present study compared to those in other national studies**

Authors	Years	City	GA (weeks) or BW (g)	Number of patients	ROP (%)
Al-Amro <i>et al.</i> <sup>[2]</sup>	2002	Riyadh	GA $\leq 34$ or BW $\leq 2000$	195	37.4
Binkhathlan <i>et al.</i> <sup>[4]</sup>	2007	Riyadh	GA $\leq 36$ or BW $\leq 2000$	174	56.0
Amer <i>et al.</i> <sup>[3]</sup>	2012	Khamis Mushait	GA $\leq 32$ or BW $\leq 1500$	386	23.3
Waheeb and Alshehri <sup>[5]</sup>	2016	Jeddah	GA $< 32$ or BW $< 1500$	92	33.7
Al-Qahtani <i>et al.</i> <sup>[6]</sup>	2019	Riyadh	GA $< 32$ or BW $< 1501$	581	38.6
Present study	2020	Jeddah	GA $\leq 32$ and/or BW $\leq 2000$	295	31.9

ROP: Retinopathy of prematurity, GA: Gestational age, BW: Birth weight

**Table 2: Characteristic of patients in the no retinopathy of prematurity and the retinopathy of prematurity groups**

	No ROP group (n=201)	ROP group (n=94)		P
		Nontreated (n=73)	Treated (n=21)	
Birth weight (g)	1158.8±246.4	980.6±244.0	767.8±152.0	<0.001*
Gestational age (weeks)	29.6±2.3	27.6±1.7	26.5±1.9	<0.001*
Length of stay in the NICU (days)	52.0±33.7	74.3±37.0	114.9±67.8	<0.001*
Weight gain at 6 weeks (g)	523.6±218.3	429.0±193.6	410.0±171.7	0.002*
Apgar score at 1 min	5.5±2.2	5.1±2.2	4.7±2.6	0.076
Apgar score at 5 min	7.8±1.5	7.5±1.7	7.7±1.6	0.153

ROP: Retinopathy of prematurity, NICU: Neonatal intensive care units

**Table 3: Univariate and multivariate logistic regression analyses of maternal risk factor for any stage retinopathy of prematurity and type 1 retinopathy of prematurity**

	OR	95% CI		P	OR	95% CI		P
		Lower	Upper			Lower	Upper	
Any stage ROP								
Chronic hypertension	0.144	0.019	1.109	0.063				
Preeclampsia	0.765	0.416	1.405	0.388				
Eclampsia	0.409	0.115	1.448	0.166				
Gestational diabetes	1.073	0.356	3.232	0.900				
Chronic diabetes	0.674	0.622	0.730	0.999				
PPROM	0.769	0.428	1.383	0.380				
Antenatal steroids	1.402	0.852	2.291	0.178				
Delivery mode (SVD)	0.598	0.358	0.998	0.049*	0.520	0.188	1.442	0.209
Type 1 ROP								
Chronic hypertension	0.774	0.694	0.864	1.000				
Preeclampsia	1.054	0.305	3.644	0.934				
Eclampsia	7.579	0.652	88.101	0.106				
Gestational diabetes	2.456	0.382	15.772	0.344				
Chronic diabetes	-	-	-	-				
PPROM	0.193	0.024	1.559	0.123				
Antenatal steroids	0.619	0.232	1.648	0.337f				
Delivery mode (SVD)	0.684	0.257	1.820	0.447				

ROP: Retinopathy of prematurity, OR: Odds ratio, CI: Confidence intervals, PPRM: Preterm premature rupture of membranes, SVD: Spontaneous vaginal delivery

with previous studies in the literature, low BW remains the single most predictive risk factor for both, any stage ROP and type 1 ROP.<sup>[10-12]</sup> This study revealed higher incidences of surfactant therapy, anemia, poor weight gain at 6 weeks, and delivery by SVD among infants with any stage ROP. Infants with type 1 ROP had a lower BW, lower GA, longer NICU stay, and a higher incidence of having IVH and BPD.

Studies regarding the incidence of ROP in the population of Saudi Arabia have reported contradictory findings [Table 1]. In our study, 31.9% of premature infants developed ROP, which is similar to what has been reported in the same region by Waheeb *et al.*<sup>[5]</sup> These rates are lower than that reported in the Central region of Saudi Arabia by Al-Qahtani *et al.*, Al-Amro *et al.*, and Binkhathlan *et al.*<sup>[2,4,6]</sup> and higher than that reported in the South-West region by Amer *et al.*<sup>[3]</sup> These discrepancies might be attributed to the fact that no national guidelines for screening of ROP has been applied in Saudi Arabia despite a standardized protocol for ROP screening has been suggested in 2018.<sup>[25]</sup>

BW and GA are the most predictive risk factors for ROP.<sup>[10-12]</sup> In our study, intrauterine growth was more important than maturity, as BW but not GA was the best predictor for any stage ROP and type 1 ROP. This was not the case in the study in China by Yau *et al.* where GA but not BW was the best predictor for any stage ROP.<sup>[12]</sup> A study in Turkey by Bas *et al.* showed that both GA and BW were independent risk factors for severe ROP.<sup>[10]</sup> Another study in India by Rao *et al.* showed increased risk of ROP in older infants with GA of 31–32 weeks, as their infants of < 28 weeks had lower survival rates.<sup>[11]</sup> These studies highlight the difference in characteristics, quality of care, and risk factors for each population.

The association between mode of delivery and ROP is controversial. Manzoni *et al.* and Sasaki *et al.* reported a positive relationship between threshold ROP and delivery by SVD.<sup>[17,26]</sup> Manzoni *et al.* attributed this to the risk of hypoxia during SVD, which could aggravate the progression of ROP, and suggested it as one of the risk factors to consider for closely following up an ROP



**Table 4: Univariate and multivariate logistic regression analyses for neonatal risk factors of any stage retinopathy of prematurity group**

	Univariate				Multivariate			
	OR	95% CI		P	OR	95% CI		P
		Lower	Upper			Lower	Upper	
Sex	0.668	0.407	1.96	0.110				
Nationality	1.415	0.864	2.318	0.167				
Multiple births	1.082	0.646	1.811	0.764				
Gestational age	0.547	0.460	0.651	<0.001*	0.736	0.582	0.931	0.011*
Birth weight	0.996	0.995	0.997	<0.001*	0.998	0.996	0.999	0.008*
Apgar score at 1 min	0.901	0.802	1.011	0.077				
Apgar score at 5 min	0.885	0.754	1.038	0.133				
Resuscitation at birth	1.147	0.659	1.996	0.627				
Weight gain at 6 weeks	0.998	0.996	0.999	0.003*	0.998	0.996	1.001	0.135
Length of stay in the NICU	1.021	1.021	1.029	<0.001*	1.013	1.004	1.022	0.005*
Anemia	2.250	1.324	3.824	0.003*	0.986	0.345	2.816	0.978
Oxygen therapy	1.917	.496	9.206	.511				
RDS	1.376	0.706	2.680	0.349				
BPD	2.615	0.854	8.009	0.092				
PDA	1.422	0.854	2.368	0.176				
IVH	1.634	0.961	2.778	0.070				
Hyperglycemia	1.676	0.909	3.090	0.098				
Surfactant	2.400	1.346	4.280	0.003*	0.748	0.262	2.135	0.587
Blood transfusion	0.822	0.496	1.364	0.449				
Insulin	2.540	0.996	6.478	0.051				

NICU: Neonatal intensive care units, OR: Odds ratio, CI: Confidence intervals, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage

**Table 5: Univariate and multivariate logistic regression analyses for neonatal risk factors in type 1 retinopathy of prematurity group**

	Univariate				Multivariate			
	OR	95% CI		P	OR	95% CI		P
		Lower	Upper			Lower	Upper	
Sex	1.379	0.520	3.661	0.519				
Nationality	0.634	0.239	1.682	0.360				
Multiple births	0.681	0.236	1.966	0.478				
Gestational age	0.675	0.498	0.916	0.012*	0.918	0.592	1.421	0.700
Birth weight	0.995	0.992	0.998	0.001*	0.995	0.991	0.999	0.009*
Apgar score at 1 min	0.929	0.748	1.154	0.077				
Apgar score at 5 min	1.086	0.803	1.468	0.133				
Resuscitation at birth	1.421	0.499	4.049	0.627				
Weight gain at 6 weeks	0.999	0.996	1.003	0.734				
Length of stay in the NICU	1.017	1.005	1.028	0.003*	1.012	1.000	1.025	0.056
Anemia	1.205	0.450	3.227	0.710				
Oxygen therapy	1.296	1.159	1.448	0.443				
RDS	1.869	0.384	9.101	0.349				
BPD	11.094	1.972	62.401	0.006*	1.516	0.117	19.683	0.750
PDA	2.560	0.951	6.891	0.063				
IVH	4.306	1.553	11.941	0.005*	5.179	1.46	18.29	0.011*
Hyperglycemia	0.663	5.638	5.638	0.227				
Surfactant	1.684	0.440	6.446	0.447				
Blood transfusion	0.852	0.306	2.372	0.759				

NICU: Neonatal intensive care units, OR: Odds ratio, CI: Confidence interval, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage

infant.<sup>[17]</sup> On the other hand, Holmström *et al.* determined no significant relationship between ROP and SVD.<sup>[27]</sup> Our study has identified that infants born by SVD were

more likely to develop any stage ROP in the univariate analysis. Based on our results, oxygenation, Apgar scores, resuscitation at birth, and neonatal morbidities were

similar between infants born using different modes of delivery. However, lower GA was found in the neonates born vaginally compared to those born by CS and since lower GA is a risk factor for ROP development, this might explain why SVD was found as a risk factor in our cohort.<sup>[10,11]</sup> In our opinion, this established relationship between SVD and ROP could be an association rather than causation. Although CS could increase the risk of maternal comorbidities, it is thought to reduce the incidence of neonatal comorbidities especially in infants born from week 23 + 0 to week 27 + 6 of GA.<sup>[16,17]</sup>

Various reports have evaluated maternal risk factors and the development of ROP.<sup>[7,13,20,27-30]</sup> It is speculated that the pathogenesis of ROP starts *in utero* and is multifactorial, but based on the current literature, antenatal risk factors still play an undetermined role.<sup>[7,9]</sup>

In our study, neither preeclampsia nor eclampsia had an increased correlation with any stage ROP or Type 1 ROP. A recent meta-analysis including 13 cohort studies related to hypertensive diseases of pregnancy found no clear relationship between ROP and hypertensive pregnancy diseases including; preeclampsia, eclampsia, and gestational hypertension; furthermore, most of these studies were found to be insufficient and subject to bias; therefore, the results remain controversial.<sup>[13]</sup> There is no concrete evidence of how hypertensive diseases of pregnancy affect ROP; however, studies that suggested that an increase of soluble fms-like tyrosine kinase-1 (sFlt-1) in the plasma of preeclamptic mothers could provide protective effect, since it is a VEGF and placental growth factor agonist which can cross the placenta.<sup>[19,20,30,31]</sup> Conversely, studies that suggested an increased risk of ROP with preeclampsia observed dysregulation of angiogenic factors associated with placental defective circulation and oxidative stress. Moreover, they reported that placental ischemia might cause retinal hypoxia and elevation of VEGF in preterm infants, thus, causing ROP.<sup>[20]</sup>

In our study, essential hypertension was observed in a few mothers with preterm births due to the nature of this chronic disease, which is usually related to advanced age.<sup>[32]</sup> Hypertension causes more pregnancy-related complications including an increased risk of preterm delivery, BW below the 10<sup>th</sup> percentile for the GA, intrauterine growth restriction, preeclampsia and a higher risk of CS delivery.<sup>[33]</sup> Although Holmström *et al.* reported a trend toward more ROP cases in mothers with preexisting chronic hypertension, we did not find that chronic hypertension was correlated with ROP.<sup>[27]</sup> This could be because in our study all hypertensive patients were delivered by CS, and CS was protective.

Other maternal risk factors like diabetes were suggested to have a role in ROP. Purohit *et al.* proposed that

babies of mothers with diabetes have higher levels of hyperglycemia, which leads to vasodilation, further stimulating neovascularization.<sup>[18]</sup> However, a study by Bental *et al.* showed no relation between gestational diabetes and severe ROP stages 3 and 4.<sup>[29]</sup> Holmström *et al.* reported no increase in any stage ROP in mothers with chronic diabetes.<sup>[27]</sup> Similarly, our reports show no increased risk of any stage ROP or Type 1 ROP that needs treatment in mothers with diabetes.<sup>[27]</sup>

Conflicting data have been published about PPROM as a risk factor. A study by Lee *et al.* and Lynch *et al.* have shown that PPROM might have a protective effect, by allowing the time for administration of steroids and antibiotics before delivery.<sup>[7,34]</sup> On the other hand, a study by Ozdemir *et al.* found that mothers with PPROM of > 18 h had an increased risk of infants with severe ROP, this was attributed to the infection and inflammation experienced during this phase.<sup>[35]</sup> Meanwhile, Holmström *et al.* reported insignificant relationship between PPROM and ROP.<sup>[27]</sup> Similarly, PPROM was neither protective nor increased the risk of ROP in our study.

Among mothers, who went into preterm delivery almost half of them, 47.5% received ANS. This point of view was supported by Bas *et al.* who reported an increase in ROP in a group of mothers that did not receive two doses of ANS.<sup>[10]</sup> It is suggested that ANS could improve systemic circulation and angiogenesis, playing a pivotal role in the maturation of the cerebral vasculature.<sup>[36]</sup> Sasaki *et al.* reported that ANS decreased the risk of mortality in extremely preterm infants as well as the risk of developing any stage ROP.<sup>[26]</sup> However, Eriksson *et al.* reported the increased risk of ROP in infants receiving ANS.<sup>[37]</sup> Our study findings were similar to those by Rao *et al.* and Yau *et al.* where no protective or predisposing ANS effect was observed.<sup>[11,12]</sup>

There are some limitations to the present study. This study was retrospective in nature. ROP screening was done by multiple ophthalmologists, causing possible inter-observer variability. The small sample size was contributed by the fact that 80% of preterm deliveries are neonates >32 weeks, whereas according to the ROP screening criteria, we only examined infants with a GA ≤ 32 weeks. Finally, we included mothers with multiple births, possibly affecting the analysis of maternal risk factors. However, this is the first study to investigate and identify maternal risk factors in Saudi Arabia. Thus, the present study could serve as a benchmark for further local studies.

## Conclusion

Lower GA, lower BW, and longer NICU stays were important predictors of any stage ROP and type 1 ROP.

Of those, lower BW was the only shared independent risk factor. This emphasizes the role of the obstetrician in antenatal care to promote better health and modify maternal risk factors that might lead to earlier deliveries with lower BW values. Moreover, there were no maternal associations, except for deliveries by SVD, which was a risk factor for any stage ROP. Additional projects are needed to monitor neonatal standards of care in local institutes in Saudi Arabia to improve ROP outcomes, and future collaborative multicenter studies are needed to enrich our understanding of the major risk factors that play a role in the pathophysiology of the disease in our region and allow us to tailor ROP managements.

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### Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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