

## Original Article

**Retinopathy of prematurity at Thammasat University Hospital**

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**Abstract**

**Background:** Retinopathy of Prematurity (ROP) is one of the major causes of retinal vascular changes and subsequent abnormal vision in children. ROP has 5 stages of severity ranging from abnormal blood vessel growth to retinal detachment. The severity of ROP depends on the gestational age and lesion location.

**Objective:** To study factors related to ROP in preterm infants

**Methods:** This descriptive study comprised 100 preterm infants with criteria of gestational age at birth of less than 37 weeks or birth weight less than 2,000 grams and born from 1 January to 31 December 2017 in Thammasat University Hospital. The neonatal data and eye examination results were recorded and analyzed.

**Results:** ROP occurred in 10 percent of 100 premature infants, and 3 percent of patients were treated. The data analysis found that the risk factors associated with ROP included low birth weight, prematurity, bronchopulmonary dysplasia, respiratory distress, and intraventricular hemorrhage which conferred significantly higher risk of ROP, while transient tachypnea of the newborn conferred significantly lower risk.

**Conclusion:** Our study provides support to previous study regarding the risk factors of ROP. Furthermore, this study shows that transient tachypnea of the newborn could act as a protective factor against ROP.

**Key Words:** Retinopathy of prematurity, Prematurity, Birth weight, Gestational age, Risk factor

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## Introduction

Retinopathy of Prematurity is one of the major causes of retinal vascular changes and subsequent abnormal vision in children. While some patients can recover without any treatment, severe conditions can occur in premature infants with incomplete development of retinal blood vessel. Upon receiving oxygen after a hypoxic condition, the surge in oxygen levels leads to changes in the retinal blood vessels and revascularization into the vitreous, which can result in partial or total retinal detachment.

ROP has 5 stages of severity ranging from abnormal blood vessel growth to retinal detachment. Its significant risk factors are premature newborn and low birth weight. From the study in the United States,<sup>1</sup> there was no ROP patient with gestational age at birth of more than 32 weeks. ROP patients with gestational age of 28 weeks and more generally do not require any surgical intervention.

The less gestational age, the greater severity of ROP it is. Studies from The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)<sup>2</sup> have shown that the average postconceptional age of ROP patients was 38.6 weeks, and 90 percent were found before the postconceptional age at 44 weeks. Moreover, for 99 percent of all patients, there was no need for treatment. The 3.1 percent of untreated patients had anatomical changes such as lesion on retinal surface and retinal detachment, and 5.1 percent of them developed more symptoms which worsened vision.<sup>1</sup> Therefore, the retinal disease surveillance and screening examination in premature infants are necessary. As mentioned, the prevention of disease was determined. This study explored ROP and the correlations between ROP and its risk factors.

## Methods

This study was a descriptive study. We collected data from the infants born at Thammasat University Hospital with criteria of gestational age at birth of less than 37 weeks or birth weight less than 2,000 grams during January to December 2017. The exclusion criteria were the infants, who had congenital anomaly, passed away or cannot do the following examination at the hospital. These infants were all referred to ophthalmologists for eye examination. However, these inclusion criteria were different from the protocol of ROP Screening of Department of Pediatrics, Thammasat University, which included infants with gestational ages at birth less than 30 weeks or birth weights less than 1,500 grams or infants with gestational age at birth more than 30 weeks with high risk.

According to the protocol of ROP Screening of Department of Pediatrics, infants with 27 weeks gestational age or less were firstly examined at postconceptional age at 31 weeks and infants with gestational age at birth more than 27 weeks were first examined at 4 weeks after birth. The following examination was set for 1-4 weeks later, depending on the severity, and then continued until retinal vascularization was complete.

Data including gestational age, birth weight, and ROP-associated comorbidities were collected from the medical record and were recorded in a checklist by a researcher.

This study was approved by the Ethics Committee of the Faculty of Medicine, Thammasat University, Thailand.

## Statistical Analysis

The number of sample size was calculated from Cochran (1973) method. Fisher's exact test was used, and SPSS was used for statistical data analyses. A *P*-value of <0.05 was considered statistically significant.

**Results**

There were 100 preterm newborns that met the criteria of study and were born at Thammasat University hospital from January 2017 to December 2017. They consisted of 48 male newborns and 52 female newborns. Their gestational ages at birth were between 25 to 36 week and birth weights were

between 724 and 2,000 grams. Ten newborns—5 males and 5 females—were diagnosed with ROP. From the data, patients with ROP had lower gestational age and less birth weight than patients without ROP (Table 1).

**Table 1** Demographic, pregnancy and neonatal data

Variable		Total (n=100) n(%)	no ROP (n=90) n(%)	ROP (n=10) n(%)	P-value
Sex	Male	48 (100)	43 (90)	5 (10)	0.167
	Female	52 (100)	47 (90)	5 (10)	
Gestational age at birth in week (Mean ± SD)		31 ± 2.8	32 ± 2.4	27.9 ± 2.2	<0.001*
Birth weight in gram (Mean ± SD)		1,491 ± 354	1,548 ± 326	1,169 ± 349	<0.001*
Mode of delivery	normal labor	43 (100)	39 (91)	4 (9)	0.524
	cesarean section	57 (100)	51 (89)	6 (11)	
Gestation	Singleton	79 (100)	71 (90)	8 (10)	0.591
	Twin	21 (100)	19 (90)	2 (10)	

ROP, Retinopathy of prematurity

It was found that gestational ages at birth of patients with ROP were between 25 weeks to 30+3 weeks. There were 5 infants (50%) with gestational age of 28 weeks or less, 4 infants (40%) with gestational age between 28 to 30 weeks, 1 infant (10%) with gestational age between 30 to 32 weeks

and no infant with gestational age of 32 weeks or more was diagnosed ROP. Lower gestational age was associated with a great number of ROP occurrences and severity of cases. All of the patients with ROP stage 3 had gestational age at birth less than 28 weeks (Table 2).

**Table 2** Gestational age and Retinopathy of prematurity staging

Gestational age (week)	Total n(%)	no ROP n(%)	ROP (stage)				OR (95% CI)	P-value
			All n(%)	1 n(%)	2 n(%)	3 n(%)		
≤28	10 (10)	5 (6)	5 (50)	0	2 (67)	3 (100)	12 (2.574 - 55.927)	<0.001*
28< GA ≤30	10 (10)	6 (7)	4 (40)	3 (75)	1 (33)	0	9.4 (2.082 - 42.838)	<0.001*
30< GA ≤32	22 (22)	21 (23)	1 (10)	1 (25)	0	0	0.44 (0.053 - 3.705)	0.479
>32	58 (58)	58 (64)	0	0	0	0	-	<0.001*
Total [n(%)]	100 (100)	90 (100)	10 (100)	4 (100)	3 (100)	3 (100)		

GA, Gestational age

ROP, Retinopathy of prematurity

The range of birth weight of ROP patients was between 762 grams and 1,810 grams. The number of patients whose birth weight less than 1,000 grams, 1,001-1,500 grams and 1,501-2,000 grams were 5, 3 and 2 patients, respectively. The larger number of ROP patients and more severe conditions were found in

patients with lower birth weight. Furthermore, all of the patients with ROP stage 3 had birth weight less than 1,000 grams (Table 3). The ROP was detected in 10 of 72 patients with a history of oxygen therapy (Table 4).

**Table 3** Birth weight and Retinopathy of prematurity staging

Birth weight (gram)	Total n(%)	no ROP n(%)	ROP (stage)				OR (95%CI)	P-value
			All n(%)	1 n(%)	2 n(%)	3 n(%)		
<1000	13 (13)	8 (9)	5 (50)	0	2 (67)	3 (100)	10.25 (2.436 - 43.113)	<0.001*
1001-1500	27 (27)	24 (26)	3 (30)	2 (50)	1 (33)	0	1.178 (0.281 - 4.929)	0.999
1501-2000	60 (60)	58 (65)	2 (20)	2 (50)	0	0	0.137 (0.027 - 0.689)	0.007*
Total [n(%)]	100 (100)	90 (100)	10 (100)	4 (100)	3 (100)	3 (100)		

ROP, Retinopathy of prematurity

**Table 4** Comparison of modes of oxygen therapy between ROP patients and no ROP patients (Some patients received oxygen through more than one mode of oxygen therapy.)

Variable	Total n(%)	no ROP n(%)	ROP (stage)			
			All n(%)	1 n(%)	2 n(%)	3 n(%)
Mechanical ventilation	16 (100)	9 (56)	7 (44)	3 (18)	2 (13)	2 (13)
Noninvasive ventilation	61 (100)	52 (85)	9 (15)	3 (5)	3 (5)	3 (5)
Nasal oxygen	72 (100)	62 (86)	10 (14)	4 (6)	3 (4)	3 (4)

ROP, Retinopathy of prematurity

From the collected data, some patients received oxygen through more than one mode of oxygen therapy (mechanical ventilation, noninvasive ventilation or nasal oxygen). The duration of oxygen therapy in non-ROP patients of mechanical ventilation, noninvasive ventilation, and nasal oxygen was  $1.3 \pm 5.4$ ,  $2.7 \pm 10.7$  and  $8.1 \pm 16$  days, respectively. The duration of oxygen therapy in ROP patients of mechanical

ventilation, noninvasive ventilation, and nasal oxygen was  $8 \pm 13.2$ ,  $3.8 \pm 6.4$  and  $25.9 \pm 29.5$  days, respectively. There were some differences between ROP patients and non-ROP patients in durations of oxygen usage. In addition the duration of oxygen therapy in patients with ROP was more than patients without ROP (Table 5).

**Table 5** Comparison of durations of oxygen therapy between ROP patients and no ROP patients

Duration of therapy (days)	no ROP		ROP		ROP (stage)		
	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD	1	2	3
Mechanical ventilation	1-42	$1.3 \pm 5.4$	1-42	$8 \pm 13.2$	1 - 13	1	1 - 42
Noninvasive ventilation	1-90	$2.7 \pm 10.7$	1-21	$3.8 \pm 6.4$	1 - 7	1	1 - 21
Nasal oxygen	1-60	$8.1 \pm 16.0$	1-75	$25.9 \pm 29.5$	1 - 70	30 - 75	1 - 48

ROP, Retinopathy of prematurity

This study has shown that the number of patients diagnosed with ROP in stage 1, stage 2 and stage 3 were 4, 3 and 3 patients, respectively. From 6 patients who were diagnosed with ROP stage 1 in the first screening examination, we found that two of them had disease progression: one patient developed ROP stage 2 and the other developed stage 3. Additionally, one of three patients who had the first detection at ROP stage 2 had disease progression to stage 3. Moreover, there was no patient diagnosed with a retinal abnormality in zone 1.

Among the ten infants with abnormal retinal disease, three had undergone laser therapy. One of them was ROP stage 2 and the other two were ROP

stage 3. The initial age upon treatment was 36 weeks. Furthermore, all of the patients with ROP stage 1 recovered without any treatments.

Fisher’s exact test (2-sided) indicated all independent variables as shown in table 6. It was found that there was statistical significance ( $P < 0.05$ ) in relations between the prevalence of ROP and bronchopulmonary dysplasia, transient tachypnea of the newborn, respiratory distress syndrome and intraventricular hemorrhage. The protective effect was transient tachypnea of the newborn, (Odds ratio [OR] 0.844, 95% CI 0.759-0.938), while the other three variables were risk factors.

Table 6 Comparison of risk factors between ROP patients and no ROP patients

Variable	Total n(%)	no ROP n(%)	ROP (stage)				OR (95% CI)	P-value
			Total n(%)	1 n(%)	2 n(%)	3 n(%)		
<b>Respiratory conditions</b>								
Bronchopulmonary dysplasia	23 (100)	14 (61)	9 (39)	4 (17)	2 (9)	3 (13)	1.622 (1.167 - 2.252)	<0.001*
Respiratory distress syndrome	48 (100)	38 (80)	10 (20)	4 (8)	3 (6)	3 (6)	1.263 (1.093 - 1.460)	<0.001*
Pneumonia	3 (100)	3 (100)	0	0	0	0	0.897 (0.838 - 0.960)	1
TTNB	36 (100)	36 (100)	0	0	0	0	0.844 (0.759 - 0.938)	0.013*
PPHN	2 (100)	2 (100)	0	0	0	0	0.898 (0.840 - 0.960)	1
Surfactant therapy	9 (100)	6 (67)	3 (33)	2 (22)	0	1 (11)	1.385 (0.869 - 2.206)	0.044*
<b>Interventions</b>								
Phototherapy	57 (100)	47 (82)	10 (18)	4 (8)	3 (5)	3 (5)	0.991 (0.869 - 1.130)	1
Blood transfusion	6 (100)	2 (33)	4 (67)	2 (33)	1 (17)	1 (17)	2.809 (0.905 - 8.719)	0.001*
<b>Obstetrics conditions</b>								
Maternal corticosteroid usage	46 (100)	40 (87)	6 (13)	4 (9)	2(4)	0	1.065 (0.930 - 1.219)	0.506
Anhydramnios	4 (100)	3 (75)	1 (25)	1 (25)	0	0	1.208 (0.684 - 2.135)	0.348
PROM	18 (100)	16 (88)	2 (12)	1 (6)	1 (6)	0	1.015 (0.850 - 1.213)	1
Preeclampsia	8 (100)	7 (88)	1 (12)	1 (12)	0	0	1.031 (0.787 - 1.351)	0.583
GDM	3 (100)	3 (100)	0	0	0	0	0.897 (0.838 - 0.960)	1
Fetal distress	4 (100)	3 (75)	1 (25)	0	1 (25)	0	1.208 (0.684 - 2.135)	0.348
Non reassuring fetal heart sound	5 (100)	4 (80)	1 (20)	1 (20)	0	0	1.132 (0.727 - 1.762)	0.416
IUGR	5 (100)	5 (100)	0	0	0	0	0.895 (0.835 - 0.959)	1

**Table 6** Comparison of risk factors between ROP patients and no ROP patients (Continue)

Variable	Total n(%)	no ROP n(%)	ROP (stage)				OR (95% CI)	P-value
			Total n(%)	1 n(%)	2 n(%)	3 n(%)		
<b>Other conditions</b>								
Hypoglycemia	13 (100)	13 (100)	0	0	0	0	0.885 (0.821 - 0.955)	0.351
Intraventricular hemorrhage	20 (100)	14 (70)	6 (30)	3 (15)	1 (5)	2 (10)	1.356 (1.013 - 1.815)	0.004*
Osteopenia of prematurity	8 (100)	5 (62)	3 (38)	0	1 (13)	2 (25)	1.478 (0.861 - 2.537)	0.031*
Anemia	31 (100)	25 (81)	6 (19)	3 (10)	1 (3)	2 (6)	1.168 (0.974 - 1.401)	0.066
Early neonatal sepsis	39 (100)	32 (81)	7 (19)	3 (8)	1 (3)	3 (8)	1.159 (0.990 - 1.356)	0.044*
Pneumothorax	3 (100)	3 (100)	0	0	0	0	0.897 (0.838 - 0.960)	1
Late neonatal sepsis	15 (100)	14 (93)	1 (7)	1 (7)	0	0	0.958 (0.821 - 1.117)	1
Patent ductus arteriosus	14 (100)	11 (79)	3 (21)	0	1 (7)	2 (14)	1.169 (0.883 - 1.548)	0.145
Necrotizing enterocolitis	5 (100)	2 (40)	3 (60)	2 (40)	0	1 (20)	2.316 (0.790 - 6.785)	0.007*

GDM, Gestational diabetes mellitus  
 IUGR, Intrauterine growth restriction  
 PPHN, Persistent pulmonary hypertension of the newborn  
 PROM, Premature rupture of membranes  
 ROP, Retinopathy of prematurity  
 TTNB, Transient tachypnea of the newborn

**Discussion**

We found the incidence of ROP in premature infants born at Thammasat University Hospital to be at 10 percent, similar to that of Siriraj Hospital<sup>3</sup> (12.9%), Songklanagarind Hospital<sup>4</sup> (15.9%) and USA<sup>5</sup> (15.58%). The difference of selection criteria may influence the incidence of ROP in premature infants of these studies.

Previous studies<sup>1, 4, 5, 6, 7, 8, 9, 10</sup> indicated that the major factors of ROP were gestational age and birth weight. In this study, the median and the mean gestational age at birth were 27.5 weeks and 27.9 ± 2.2 weeks, respectively, compared to a median gestational age at birth of 25 weeks for a study in the United Kingdom.<sup>6</sup> The mean age from the study in Songklanagarind Hospital<sup>4</sup> was 28.4 ± 2.4 weeks which was similar to this study.

In our study, 50% of ROP patients had gestational age at birth equal or less than 28 weeks, which is in accordance with the result from Smith-Kettlewell Eye Research Institute, San Francisco, USA<sup>7</sup> at which 47% of ROP patients had gestational age at birth of less than 27 weeks. Meanwhile, the study at Songklanagarind Hospital<sup>4</sup> found that there were 73 percent of ROP patients with gestational age at birth of less than 28 weeks. There was no ROP patient who has gestational age at birth of more than 32 weeks—a similar finding to the study from the University of Connecticut School of Medicine, Connecticut, USA.<sup>8</sup>

The mean and the median birth weight in this study were  $1,169 \pm 349$  grams and 1,079 grams, respectively, compared to the study in Germany<sup>11</sup> and Songklanagarind Hospital<sup>4</sup> at which the mean birth weight was  $991 \pm 225$  and  $1,158 \pm 365$  grams and the study in the United Kingdom<sup>6</sup> at which the median birth weight was 706 grams. Birth weight average is likely lower in Europe due to higher survival rates of premature infants. From this study, it was found that 50 percent of ROP patients had birth weight less than 1,000 grams, which is similar to the number from Songklanagarind Hospital study.<sup>4</sup> Infants with lower birth weight seemed to have a greater chance of disease.

The correlation between oxygen and ROP was documented in previous studies.<sup>12, 13, 14, 15, 16, 17, 18</sup> High oxygen intake leads to decreasing vascularization and vessel constriction, resulting in retinal ischemia. Statistical analyses showed that bronchopulmonary dysplasia, respiratory distress, and intraventricular hemorrhage had a significant higher risk for ROP similar to the study from University of Pennsylvania, USA.<sup>9</sup> However, it was interesting that infants with ROP had a lower association with transient tachypnea of the newborn which was one of the respiratory diseases. Both bronchopulmonary dysplasia and respiratory distress were conditions associated with prolonged oxygen exposure; nonetheless, transient tachypnea of the newborn was treated with shorter duration of oxygen therapy. In addition, from the oxygen usage data, we found that 28 preterms without oxygen therapy had no ROP. The greater number of mean oxygen usage duration of ROP patients, the more incidences of ROP occur. Intraventricular hemorrhage is also a major complication of prematurity that might involve the risk of ROP. The Stanford University School of Medicine study in California, USA<sup>5</sup> found that the significant lower risks of ROP were necrotizing enterocolitis and hypoxia. Furthermore, the study from Germany<sup>11</sup> found that infants with necrotizing enterocolitis

and infants with a history of maternal preeclampsia developed ROP less often; on the contrary, these factors were not associated with a lower ROP incidence in this study.

The study in the United Kingdom<sup>6</sup> and Germany<sup>18</sup> has shown that the number of the treated patient was 4 and 3.2 percent, respectively, which similar to this study (3 percent). All of the treated patients in this study had gestational age at birth less than 28 weeks same as the study from Christchurch School of Medicine, Christchurch.<sup>10</sup> Moreover, no patient with gestational age 28 weeks and more underwent laser therapy, in contrast to the study in Switzerland<sup>19</sup> that 0.06 percent of the treated patient had gestational age more than 29 weeks.

The current guideline is appropriate in term of the optimal time to initiate the first screening test but should be consider the proper criteria of birth weight. Owing to the criteria for screening eye examination at Thammasat University Hospital which were infants with their gestational age at birth less than 30 weeks or their birth weight less than 1,500 grams or infants with gestational age at birth more than 30 weeks with high risk. As mentioned previously, this study found 2 percent of ROP patient whose birth weight between 1,500 and 2,000 grams. Therefore, one patient was firstly diagnosed ROP stage 1 at gestational age 31 + 4 weeks then the lesion recovered itself after the following examination at postconceptional age 46 + 5 weeks. According to treatment guideline, the ophthalmologist does the first retinal examination at 4 weeks after birth (chronological age) or postconceptional age at 31 weeks by choosing the latest time. Another patient with gestational age 27 + 5 weeks at birth was examined late at postconceptional age 38 weeks due to respiratory complication. His right eye developed ROP stage 1, zone III then progressed to ROP stage 2, zone III and the other had ROP stage 2, zone III. After the follow-up examination until postconceptional age 47 weeks, the disease recovered without any treatments.



### Discussion

The presence of ROP was significantly high related to low birth weight, prematurity, bronchopulmonary dysplasia, respiratory distress, and intraventricular hemorrhage, conversely, transient tachypnea of the newborn had lower association with ROP. ROP is preventable. Major cause of blindness in children was affected by many associated comorbidities. Therefore, the proper screening test should be mandatory.

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### บทคัดย่อ

โรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนดที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

ชนิกานต์ ภูวิชัยสัมฤทธิ์

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**ภูมิหลัง :** โรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนดมีความรุนแรงหลายระดับโดยขึ้นอยู่กับอายุครรภ์และตำแหน่งรอยโรคและมีปัจจัยที่เกี่ยวข้อง ได้แก่ ทารกเกิดก่อนกำหนด ภาวะขาดออกซิเจน การได้รับออกซิเจน อายุครรภ์น้อย น้ำหนักแรกคลอดน้อย เป็นต้น

**วัตถุประสงค์ :** เพื่อศึกษาปัจจัยที่เกี่ยวข้องกับการเกิดโรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนด

**วิธีการ :** ศึกษาข้อมูลจากเวชระเบียนของทารกเกิดที่อายุครรภ์  $\leq 37$  สัปดาห์หรือทารกที่มีน้ำหนักแรกเกิด  $\leq 2,000$  กรัม และเป็นผู้ป่วยที่คลอดและรับการตรวจและรักษาโรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนดที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ โดยเกิดตั้งแต่ 1 มกราคม 2560 - 31 ธันวาคม 2560 กำหนดขนาดตัวอย่างเท่ากับ 100 ตัวอย่าง

**ผลการศึกษา :** พบว่าทารก 100 ราย เป็นโรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนดทั้งหมด 10 ราย คิดเป็นร้อยละ 10 โดยทารก 3 ราย ต้องได้รับการรักษาโรคจอประสาทตามืดปรกติแต่กำเนิดด้วยการใช้เลเซอร์ และพบปัจจัยเสี่ยงที่มีความสัมพันธ์กับการเกิดโรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนดอย่างมีนัยสำคัญ ( $P < 0.05$ ) ได้แก่ ทารกแรกเกิดน้ำหนักน้อย ทารกเกิดก่อนกำหนด, การเกิดภาวะปอดเรื้อรัง, ภาวะหายใจลำบากและภาวะเลือดออกในสมองในเด็กเกิดก่อนกำหนด และปัจจัยที่ทำให้มีอัตราการเกิดโรคน้อยลง คือ ภาวะกลุ่มอาการหายใจลำบากช่วงหนึ่งในทารกแรกเกิด

**สรุป :** จากการศึกษาพบว่าความเสี่ยงในการเกิดโรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนดสอดคล้องกับผลการศึกษาที่ผ่านมาและพบว่าภาวะกลุ่มอาการหายใจลำบากช่วงหนึ่งในทารกแรกเกิดเป็นปัจจัยป้องกันการเกิดโรค

**คำสำคัญ:** โรคจอประสาทตามืดปรกติในทารกเกิดก่อนกำหนด, ทารกเกิดก่อนกำหนด, น้ำหนักแรกเกิด, อายุครรภ์แรกเกิด, ปัจจัยเสี่ยง