Preeclampsia and Retinopathy of Prematurity in Very-Low-Birth-Weight Infants: A Population-Based Study

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Abstract

Preeclampsia and retinopathy of prematurity (ROP) are associated with impaired angiogenesis. Previous studies on the relationship between preeclampsia and ROP have produced conflicting results. The goal of this study was to evaluate the association between maternal preeclampsia and ROP using a large population-based cohort of very-low-birth-weight (VLBW) infants from 21 neonatal departments registered in the database of the Premature Baby Foundation of Taiwan. Multivariable logistic regression analysis was used to estimate the adjusted odds ratios (OR) and 95% confidence intervals (CI) for preeclampsia with reference to ROP and severe ROP. A total of 5,718 VLBW infants (844 cases with maternal preeclampsia) were included for analysis. The overall incidences of mild and severe ROP were 36.0% and 12.2%, respectively. Univariable analysis showed lower GA and lower birth weight, vaginal delivery, non-SGA, RDS, PDA, sepsis, transfusion, and absence of maternal preeclampsia to be associated with mild and severe ROP development. However, OR (95% CI) adjusted for the variables that were significant according to univariable analysis showed the risks of developing any-stage ROP and severe ROP for maternal preeclampsia to be 1.00 (0.84–1.20) and 0.89 (0.63–1.25), respectively. The results remained unchanged in stratified analyses according to SGA status. Our data showed that maternal preeclampsia was not associated with the subsequent development of any stage or severe ROP in VLBW infants.
Introduction

Retinopathy of prematurity (ROP), a disease associated with abnormal retinal vascular development in preterm infants [1], occurs frequently among very preterm infants [2, 3]. With the improved survival of this population due to advances in neonatal care, ROP has become a leading cause of childhood blindness worldwide [4]. Several risk factors, including small gestational age, low birth weight, and postnatal oxygen therapy, are known to be associated with the development of ROP [5, 6]. Preeclampsia causes maternal and fetal morbidity and is also a leading cause of preterm delivery of VLBW infants [7, 8]. Dysregulation of circulating antiangiogenic factors plays an important role in the pathogenesis of both preeclampsia and ROP [9, 10]. Previous studies have analyzed the relationship between maternal preeclampsia and ROP in preterm infants; however, the results have been inconsistent and conflicting due in part to the relatively small sample sizes of the studies [11–17].

Recently, 3 large-scale studies analyzing the association between preeclampsia and ROP have produced inconsistent results. Yu et al. found an association between preeclampsia and a significantly reduced risk of ROP in preterm infants.[18] However, they did not adjust for SGA, which was more common in the maternal preeclampsia group and was significantly associated with ROP [18–20]. Araz-Ersan et al. demonstrated that maternal preeclampsia was associated with decreased incidence of progression to severe ROP, but not the onset of ROP. [21]. In addition, they did not adjust their findings for other confounding factors. Lee et al. reported that maternal preeclampsia was not associated with any stage of ROP in Extremely Low Gestational Age Newborns. However, extremely preterm infants born to mothers with preeclampsia, which is associated with neonatal hyperoxemia and bacterial infection, have an increased risk of severe ROP [22]. Because of the numerous discrepancies in previous studies, we examined the association between maternal preeclampsia and ROP in a large population-based cohort of very-low-birth-weight (VLBW) infants. The goal was to demonstrate the independent association between the two variables. We also performed subgroup analysis based on SGA status, which was shown in previous studies to be strongly associated with both maternal preeclampsia and ROP.

Methods

Study subjects

A total of 8,652 VLBW infants were registered in the database of the Premature Baby Foundation of Taiwan between 1997 and 2006. All 21 NICUs in Taiwan participated in this project, making the data a truly population-based cohort. The data collected included prenatal, perinatal, and postnatal demographic and clinical variables. Patient information obtained by the database coordinator was cross-checked with our national birth registry. The exclusion criteria included GA above 36 weeks, congenital or chromosome anomalies, infants who died before the screening of ROP, and those whose ROP status was not available. The percentages of infants excluded because the ROP status was not available were 0.4% in the non-preeclampsia group and 10.9% in the preeclampsia group. There were no differences in GA, BW, incidence of transfusion requirement, or sepsis in the two groups that were excluded for analysis. In addition, infants with maternal chronic hypertension were also excluded. Preeclampsia was defined as a diastolic blood pressure of greater than 90 mm Hg accompanied by proteinuria of at least 1+ (30 mg per deciliter) on dipstick test or nondependent edema during pregnancy. The gestational age (GA) was dated by the last menstrual period or the date of embryo transfer for in vitro fertilization. The ROP status was determined by pediatric ophthalmologists in each hospital.
Ethics Statement

Written informed consent was obtained from the parents or designated relatives of the infants in the study. The study was approved by the Institutional Review Board of National Taiwan University Hospital and the Joint Institutional Review Boards of Taipei City Hospital, Cathay General Hospital, Younghe Cardinal Tien Hospital, Shin Kong Wu Ho-Su Memorial Hospital, Taipei Veterans General Hospital, Taipei Chang Gung Memorial Hospital, Tri-Service General Hospital, Mackay Memorial Hospital, China Medical University Hospital, Chung Shan Medical University Hospital, Taichung Veterans General Hospital, Changhua Christian Hospital, National Cheng Kung University Hospital, Chi Mei Hospital, Sin-Lau Hospital, Kuo General Hospital, Chia-Yi Christian Hospital, Kaohsiung Veterans General Hospital, Kaohsiung Chang Gung Memorial Hospital, and Kaohsiung Medical University Chung-Ho Memorial Hospital.

Outcome variables

Mild and Severe ROP were defined using the criteria of an international committee [23]. Severe ROP was defined as stage 3 ROP plus any disease, and stage 4 or 5 ROP [23]. Respiratory distress syndrome (RDS) was defined by clinical diagnosis and need for surfactant therapy. Necrotizing enterocolitis (NEC) was defined according to the criteria of Bell [24]. Small for gestational age (SGA) was defined as birth weight of less than the 10th percentile for the gestational age [25]. Transfusion was defined as requiring PRBC transfusion. Sepsis was defined as clinical sepsis with proof of causative agent in the blood culture. PDA required treatment means PDA required indomethacin/ibuprofen treatment or surgical ligation.

Statistical analysis

The chi-square test and Student’s $t$-test were used for comparing distributions of categorical variables and the continuous variables between groups, respectively. A multivariable logistic regression model was used to analyze the association between maternal preeclampsia and ROP risk, adjusted for variables that were found to be statistically significant by univariate analysis. Adjusted odds ratio (OR) and 95% confidence interval (CI) were derived to assess the magnitude of the association between various factors and ROP risk. We performed a similar analysis to evaluate the association between maternal preeclampsia and ROP in subgroups of different severities of ROP (mild ROP, severe ROP, ROP without therapy, and ROP requiring therapy). Statistically significant levels were determined by the 2-tailed test ($p<0.05$). The association between preeclampsia and ROP was further examined in subgroup analysis with stratification according to SGA status.

Results

A total of 5,718 VLBW infants, including 844 (14.8%) cases with maternal preeclampsia, were included for analysis. The numbers (overall incidence) of mild and severe ROP were 2,087 (36.5%) and 698 (12.2%), respectively. Infants born to a mother with preeclampsia were more likely to have higher gestational age, higher maternal age, delivery via Cesarean section, female gender, singleton, higher Apgar score at 5 minutes, and small for gestational age (SGA). They were less likely to have respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), sepsis, and transfusion. The incidence of ROP was significantly lower in infants with maternal preeclampsia than in those without maternal preeclampsia (41.4% vs. 50%) (Table 1).

Multivariable logistic analysis, which included preeclampsia, GA, birth weight (BW), Cesarean section, sex of baby, SGA, RDS, PDA, sepsis, transfusion, and Apgar score at 5 min as predictors, showed that the preeclampsia was not associated with all grade ROP (odds ratio (95%
CI) of 1.00 (0.84–1.20)). GA (0.81 (0.77–0.85)), Cesarean section (0.84 (0.74–0.95)), SGA (1.25 (1.01–1.55)), Apgar score at 5 minutes (0.75 (0.65–0.86)), transfusion (1.26 (1.11–1.44)), PDA (1.44 (1.26–1.64)), and sepsis (0.84 (0.73–0.96)) were associated with ROP (Table 2). Multivariable logistic regression analysis of different ROP severity showed that preeclampsia was not associated with either mild ROP (1.03 (0.86–1.24)) or severe ROP (0.89 (0.63–1.25)). Only GA (0.67 (0.61–0.73)), BW (0.83 (0.77–0.90), Apgar score at 5 minutes (0.81 (0.66–1.00)), and PDA (1.28 (1.04–1.57)) were associated with severe ROP (Table 3).

Since SGA was strongly associated with preeclampsia and ROP, we further performed subgroup multivariate-adjusted analysis with stratification according to SGA status. Maternal preeclampsia was not related with ROP in either the SGA group (0.98 (0.78–1.3), P = 0.8329) or the non-SGA group (1.06 (0.78–1.43), P = 0.7177). The risk factors of ROP included small GA, small BW, vaginal delivery, Apgar score at 5 minutes below 7, transfusion, PDA, and non-sepsis VLBW. In the SGA group, the risk factors of ROP, except for BW, Apgar score at 5 minutes below 7, and sepsis, were similar those in the non-SGA group (Table 4).

Because of the known phenomenon that ROP occurs almost exclusively in infants < 34 weeks, we analyzed the data of 5,296 VLBW infants of < 34 weeks, including 717 (13.5%) with maternal preeclampsia. The numbers (incidence) of mild ROP and severe ROP were 2,006 (37.9%) and 692 (13.1%), respectively. The incidence of ROP was significantly decreased in

### Table 1. Demographic and clinical variables in infants born to mothers with or without preeclampsia.

| Parameter                      | No preeclampsia N = 4874 | Preeclampsia N = 844 | P value |
|-------------------------------|--------------------------|----------------------|---------|
| Gestational age               | 29.04 (2.66)             | 30.97 (2.44)         | <0.0001 |
| Birth weight                  | 1161 (237)               | 1161 (245)           | 0.9702  |
| Maternal age                  | 29.60 (5.37)             | 31.54 (5.11)         | <0.0001 |
| Cesarean section*             | 2713 (56.0%)             | 774 (91.9%)          | <0.0001 |
| Male sex†                     | 2530 (52.1%)             | 388 (46.2%)          | 0.0017  |
| SGA                           | 1263 (25.9%)             | 619 (73.3%)          | <0.0001 |
| Singleton§                    | 3538 (72.8%)             | 716 (85.2%)          | <0.0001 |
| Antenatal steroid ≥ 2 doses†† | 1364 (32.4%)             | 217 (29.6%)          | 0.1286  |
| RDS**                         | 2213 (46.0%)             | 261 (31.7%)          | <0.0001 |
| Transfusion                   | 3070 (63.0%)             | 424 (50.2%)          | <0.0001 |
| PDA requiring treatment††     | 1708 (35.2%)             | 209 (24.9%)          | <0.0001 |
| Sepsis§§                      | 1220 (25.1%)             | 174 (20.7%)          | 0.0062  |
| Apgar score at 5 min ≥ 7‡‡     | 3092 (67.5%)             | 614 (73.9%)          | 0.0003  |
| ROP                           | 2436 (50.0%)             | 349 (41.4%)          | <0.0001 |
| Days on IPPV                  | 14.6 (26.3)              | 7.3 (15.3)           | <0.001  |
| Days on oxygen, CPAP, or IPPV | 41.9 (38.3)              | 26.3 (29.3)          | <0.001  |
| Duration of hospitalization   | 73.8 (35.9)              | 61.8 (27.6)          | <0.001  |

Data was presented as mean (SD) or number (%).

Abbreviations: SGA, small for gestational age; RDS, respiratory distress syndrome with surfactant treatment; PDA, patent ductus arteriosus.

*A total of 27 subjects were missing on this variable.
†A total of 17 subjects were missing on this variable.
§A total of 20 subjects were missing on this variable.
**A total of 86 subjects were missing on this variable.
††A total of 24 subjects were missing on this variable.
‡‡A total of 309 subjects were missing on this variable.

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infants with maternal preeclampsia (45% vs. 51.9%, P = 0.001). Again, multivariable analysis demonstrated that maternal preeclampsia was not associated with ROP (1.03 (0.85–1.25)), mild ROP (1.14 (0.85–1.54)), or severe ROP (1.00 (0.71–1.41)). Finally, when we focused on those extremely low birth weight (ELBW, birth weight below 1,000 gm) infants, multivariable polytomous analysis still showed that maternal preeclampsia was not associated with ROP (adjusted OR 0.89 (0.61–1.29)).

Discussion

Our population-based large cohort study showed that maternal preeclampsia was not associated with ROP risk in VLBW infants. This finding is consistent with the study by Lee et al., which showed that preeclampsia itself was not associated with ROP in ELGANs [22]. In addition, our data also support the findings of other studies showing that lower GA, NSD, SGA, PDA, sepsis, transfusion, and lower Apgar score at 5 minutes are associated with ROP [12–19, 21, 22, 26–29].

| Parameter                      | Odds ratio (95% CI) | P value |
|--------------------------------|--------------------|---------|
| Preeclampsia (yes vs. no)      | 1.00 (0.84–1.20)   | 0.9884  |
| Gestational age (per week)     | 0.81 (0.77–0.85)   | <.0001  |
| Birth weight, per 100 grams    | 0.92 (0.88–0.97)   | 0.0005  |
| Cesarean section (yes vs. no)  | 0.84 (0.74–0.95)   | 0.0064  |
| Sex of baby (male vs. female)  | 1.09 (0.96–1.23)   | 0.1725  |
| SGA (yes vs. no)               | 1.25 (1.01–1.55)   | 0.0407  |
| Apgar score at 5 min (>7 vs. <7)| 0.75 (0.65–0.86)   | <.0001  |
| RDS (yes vs. no)               | 0.93 (0.81–1.07)   | 0.3222  |
| Transfusion (yes vs. no)       | 1.26 (1.11–1.44)   | 0.0005  |
| PDA (required treatment vs. no)| 1.44 (1.26–1.64)   | <.0001  |

Abbreviations: SGA, small for gestational age; RDS, respiratory distress syndrome with surfactant treatment; PDA, patent ductus arteriosus.

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| Parameter                      | Mild ROP vs. no ROP | Severe ROP vs. no ROP |
|--------------------------------|---------------------|-----------------------|
| Preeclampsia (yes vs. no)      | 1.03 (0.86–1.24)    | 0.89 (0.63–1.25)      |
| Gestational age (per week)     | 0.84 (0.80–0.89)    | 0.67 (0.61–0.73)      |
| Birth weight, per 100 grams    | 0.95 (0.91–1.00)    | 0.83 (0.77–0.90)      |
| Cesarean section (yes vs. no)  | 0.85 (0.74–0.97)    | 0.83 (0.68–1.02)      |
| Sex of baby (male vs. female)  | 1.09 (0.96–1.23)    | 1.11 (0.91–1.35)      |
| SGA (yes vs. no)               | 1.19 (0.95–1.49)    | 1.35 (0.95–1.93)      |
| Apgar score at 5 min (>7 vs. <7)| 0.74 (0.64–0.85)    | 0.81 (0.66–1.00)      |
| RDS (yes vs. no)               | 0.88 (0.76–1.01)    | 1.19 (0.96–1.49)      |
| Transfusion (yes vs. no)       | 1.32 (1.15–1.52)    | 1.10 (0.88–1.38)      |
| PDA (yes vs. no)               | 1.48 (1.29–1.70)    | 1.28 (1.04–1.57)      |
| Sepsis (yes vs. no)            | 0.81 (0.70–0.94)    | 0.92 (0.75–1.14)      |

Abbreviations: SGA, small for gestational age; RDS, respiratory distress syndrome with surfactant treatment; PDA, patent ductus arteriosus.

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Preeclampsia occurs in 2%-7% of pregnancies worldwide and results in fetal and maternal morbidity [8, 30]. Increasing circulating soluble Flt-1, a soluble form of vascular endothelial growth factor (VEGF) receptor-1, which can bind both VEGF and placental growth factor (PGF), plays an important role in the pathogenesis of preeclampsia [31–34]. VEGF signaling also plays a critical role in the pathogenesis of ROP, and anti-VEGF therapy has been shown to have significant benefits in ROP treatment [35, 36]. Several reports have produced inconsistent results on the association between maternal preeclampsia and ROP [11–17]. Recently, 2 large-scale studies reported that maternal preeclampsia significantly reduced the incidence of ROP in preterm infants [18, 21]. However, they did not adjust for SGA, which is strongly associated with both preeclampsia and ROP [18–20]. In agreement with the studies by Yu et al. and Araz-Ersan et al., we found in this large multicenter study that VLBW infants delivered by mothers with preeclampsia had significantly lower incidence of ROP. However, after adjusting for confounding factors, including SGA and GA, we demonstrated that maternal preeclampsia was not associated with the risk of ROP in VLBW infants. Nonetheless, with the large sample size, we were able to do the subgroup analysis according to the SGA status, GA groups, or severity of ROP. Again, multivariate logistic regression analysis showed that maternal preeclampsia was not associated with ROP in either the SGA group or the non-SGA group, or in various GA strata, nor was maternal preeclampsia associated with either mild ROP or severe ROP. These findings suggest that although preterm infants born to mothers with preeclampsia have significantly lower incidence of ROP, maternal preeclampsia itself is not a protective factor, which is supported by a report from Lee et al. [22]. However, because potential bias such as small GA, low birth weight, and SGA may contribute to both preeclampsia and ROP, it is difficult to study an independent association between maternal preeclampsia and ROP.

The strength of our study is that it was a large multicenter population-based cohort study with several subgroup analyses, allowing us to assess the association between maternal preeclampsia and ROP. However, our study also had some limitations. First, some data of interest were unavailable (see tables). However, the large size of our database and the absence of differential misclassification would minimize these influences. Second, our cohort included only infants of birth weight below 1,500 gm, so data on larger infants born above 30 weeks’ gestation are not available, and thus infants born SGA are overrepresented in this group. However, we performed several subgroup analyses to minimize this bias.
Conclusions
Although there was potential bias of a link between preeclampsia and ROP, our large population-based retrospective analysis found no association between these two diseases.

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Author Contributions
Conceived and designed the experiments: HCH HIY PNT. Analyzed the data: HIY. Contributed reagents/materials/analysis tools: H-CH H-IY P-NT. Wrote the paper: HCH HIY PNT. Interpretation of the data: HCH HIY HCC CYC WSH KIT PNT. Approved the final version: HCH HIY HCC CYC WSH KIT PNT.

References
1. Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Quintos M, et al. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. Pediatrics. 2005; 116(1):15–23. PMID: 15995025.
2. Ancel PY, Goffinet F, Group E-W, Kuhn P, Langer B, Matis J, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. JAMA pediatrics. 2015; 169(3):230–8. doi: 10.1001/jamapediatrics.2014.3351 PMID: 25621457.
3. Lad EM, Hernandez-Boussard T, Morton JM, Moshefgh DM. Incidence of retinopathy of prematurity in the United States: 1997 through 2005. American journal of ophthalmology. 2009; 148(3):451–8. doi: 10.1016/j.ajo.2009.04.018 PMID: 19541285.
4. Gilbert C, Awan H. Blindness in children. BMJ. 2003; 327(7418):760–1. PMID: 14525849.
5. Flynn JT, Bancalari E, Snyder ES, Goldberg RN, Feuer W, Cassady J, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. New England Journal of Medicine. 1992; 326(16):1050–4. PMID: 1549150.
6. Giannantonio C, Papacci P, Molle F, Lepore D, Gallini F, Romagnoli C. An epidemiological analysis of retinopathy of prematurity over 10 years. Journal of Pediatric Ophthalmology & Strabismus. 2008; 45(3):162–7. PMID: 18524194.
7. Gyarmsi-Bannerman C, Fuchs KM, Young OM, Hoffman MK. Nonsousse late preterm birth: etiology and outcomes. American Journal of Obstetrics & Gynecology. 2011; 205(5):456.e1–6. PMID: 22035950.
8. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010; 376(9741):631–44. PMID: 20598363. doi: 10.1016/S0140-6736(10)60279-9
9. Hartnett ME. Pathophysiology and Mechanisms of Severe Retinopathy of Prematurity. Ophthalmology. 2015; 122(1):200–10. doi: 10.1016/j.ophtha.2014.07.050 PMID: 25444347; PubMed Central PMCID: PMC4277936.
10. Levine RJ, Karumanchi SA. Circulating angiogenic factors in preeclampsia. Clinical Obstetrics & Gynecology. 2005; 48(2):372–86. PMID: 15905796.
11. Cetinkaya M, Ozkan H, Koksal N, Karali Z, Ozgur T. Neonatal outcomes of premature infants born to preeclamptic mothers. Journal of Maternal-Fetal & Neonatal Medicine. 2010; 23(5):425–30. PMID: 19670043.

12. Fortes Filho JB, Costa MC, Eckert GU, Santos PGB, Silveira RC, Prociunoy RS. Maternal preeclampsia protects preterm infants against severe retinopathy of prematurity. Journal of Pediatrics. 2011; 158(3):372–6. PMID: 20888573. doi: 10.1016/j.jpeds.2010.08.051

13. Mehmet S, Fusun A, Sebnem C, Ozgur O, Gulten E, Taylan OA, et al. One-year experience in the retinopathy of prematurity: frequency and risk factors, short-term results and follow-up. International journal of ophthalmology. 2011; 4(6):634–40. doi: 10.3980/j.issn.2222-3959.2011.06.12 PMID: 22553735; PubMed Central PMCID: PMC3340803.

14. Ozkan H, Cetinkaya M, Koksal N, Ozmen A, Yildiz M. Maternal preeclampsia is associated with an increased risk of retinopathy of prematurity. Journal of Perinatal Medicine. 2011; 39(5):523–7. PMID: 21878037. doi: 10.1515/JPM.2011.071

15. Seibert V, Linderkamp O. Risk factors in retinopathy of prematurity. a multivariate statistical analysis. Ophthalmologica. 2000; 214(2):131–5. PMID: 10720918.

16. Shah VA, Yeo CL, Ling YLF, Ho LY. Incidence, risk factors of retinopathy of prematurity among very low birth weight infants in Singapore. Annals of the Academy of Medicine, Singapore. 2005; 34(2):169–78. PMID: 15827664.

17. Yang C-Y, Lien R, Yang P-H, Chu S-M, Hsu J-F, Fu R-H, et al. Analysis of incidence and risk factors of retinopathy of prematurity among very-low-birth-weight infants in North Taiwan. Pediatrics & Neonatology. 2011; 52(6):321–6. PMID: 22192259.

18. Yu XD, Branch DW, Karumanchi SA, Zhang J. Preeclampsia and retinopathy of prematurity in preterm births. Pediatrics. 2012; 130(1):e101–7. PMID: 22665405. doi: 10.1542/peds.2011-3881

19. Dhaliwal CA, Fleck BW, Wright E, Graham C, McIntosh N. Retinopathy of prematurity in small-for-gestational age infants compared with those of appropriate size for gestational age. Archives of disease in childhood Fetal and neonatal edition. 2009; 94(3):F193–5. doi: 10.1136/adc.2008.143552 PMID: 18786959.

20. Yen TA, Yang HI, Hsieh WS, Chou HC, Chen CY, Tsou KI, et al. Preeclampsia and the risk of broncho-pulmonary dysplasia in VLBW infants: a population based study. PloS one. 2013; 8(9):e75168. doi: 10.1371/journal.pone.0075168 PMID: 24073247; PubMed Central PMCID: PMC3779258.

21. Araz-Ersan B, Kir N, Akarca Y, Aydinoglu-Candan O, Sahingolu-Keskek N, Demirel A, et al. Epidemiological analysis of retinopathy of prematurity in a referral centre in Turkey. The British journal of ophthalmology. 2013; 97(1):15–7. doi: 10.1136/bjophthalmol-2011-301411 PMID: 23215061.

22. Lee JW, McElrath T, Chen M, Wallace DK, Allred EN, Leviton A, et al. Pregnancy disorders appear to modify the risk for retinopathy of prematurity associated with neonatal hyperoxemia and bacteremia. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013; 26(8):811–8. doi: 10.3109/14767058.2013.764407 PMID: 23297894; PubMed Central PMCID: PMC4167637.

23. International Committee for the Classification of Retinopathy of P. The International Classification of Retinopathy of Prematurity revisited. Archives of ophthalmology. 2005; 123(7):991–9. doi: 10.1001/archopht.123.7.991 PMID: 16009843.

24. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatric Clinics of North America. 1986; 33(1):179–201. PMID: 3081865.

25. Mikolajczyk RT, Zhang J, Betran AP, Souza JP, Mori R, Gulmezoglu AM, et al. A global reference for fetal-weight and birthweight percentiles. Lancet. 2011; 377(9780):1855. doi: 10.1016/S0140-6736(11)60364-4 PMID: 21878037.

26. Holmstrom G, Broberger U, Thomassen P. Neonatal risk factors for retinopathy of prematurity—a population-based study. Acta Ophthalmologica Scandinavica. 1998; 76(2):204–7. PMID: 9591954.

27. Wikstrand MH, Hard AL, Niklasson A, Smith L, Lofqvist C, Hellstrom A. Maternal and neonatal factors associated with poor early weight gain and later retinopathy of prematurity. Acta paediatrica. 2011; 100(12):1526–33. doi: 10.1111/j.1651-2227.2011.02394.x PMID: 21726282.

28. Zin A, Gole GA. Retinopathy of prematurity-incidence today. Clinics in perinatology. 2013; 40(2):185–200. doi: 10.1016/j.clp.2013.02.001 PMID: 23719304.

29. Walker JJ. Pre-eclampsia. Lancet. 2000; 356(9237):1260–5. PMID: 11072961.
31. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. [Erratum appears in N Engl J Med. 2006 Oct 26;355(17):1840]. New England Journal of Medicine. 2006; 355(10):992–1005. PMID: 16957146.

32. Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. New England Journal of Medicine. 2004; 350(7):672–83. PMID: 14764923.

33. Maynard SE, Venkatesha S, Thadhani R, Karumanchi SA. Soluble Fms-like tyrosine kinase 1 and endothelial dysfunction in the pathogenesis of preeclampsia. Pediatric research. 2005; 57(5 Pt 2):1R–7R. PMID: 15817508.

34. Noori M, Donald AE, Angelakopoulou A, Hingorani AD, Williams DJ. Prospective study of placental angiogenic factors and maternal vascular function before and after preeclampsia and gestational hypertension. [Erratum appears in Circulation. 2011 Sep 13;124(11):e302]. Circulation. 2011; 122(5):478–87. PMID: 20644016. doi: 10.1161/CIRCULATIONAHA.109.895458

35. Cavallaro G, Filippi L, Bagnoli P, La Marca G, Cristofori G, Raffaeli G, et al. The pathophysiology of retinopathy of prematurity: an update of previous and recent knowledge. Acta ophthalmologica. 2014; 92(1):2–20. doi: 10.1111/aos.12049 PMID: 23617889.

36. Mintz-Hittner HA, Kennedy KA, Chuang AZ, Group B-RC. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. New England Journal of Medicine. 2011; 364(7):603–15. PMID: 21323540. doi: 10.1056/NEJMoa1007374