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Prenatal and Postnatal Inflammation-Related Risk Factors for Retinopathy of Prematurity

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Abstract

Objective: To evaluate the relationship between prenatal and postnatal inflammation-related risk factors and severe retinopathy of prematurity (ROP).

Study Design: The study included infants born <30 weeks in California from 2007–2011. Multivariable log binomial regression was used to assess the association between prenatal and postnatal inflammation-related exposures and severe ROP, defined as stage 3–5 or surgery for ROP.

Results: Of 14,816 infants, 10.8% developed severe ROP. Though prenatal inflammation-related risk factors were initially associated with severe ROP, after accounting for the effect of these risk factors on gestational age at birth through mediation analysis, the association was non-significant (P=0.6). Postnatal factors associated with severe ROP included prolonged oxygen exposure, sepsis, intraventricular hemorrhage, and necrotizing enterocolitis.

Conclusion: Postnatal inflammation-related factors were associated with severe ROP more strongly than prenatal factors. The association between prenatal inflammation-related factors and ROP was explained by earlier gestational age in infants exposed to prenatal inflammation.

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Author Contributorship

All authors contributed substantially to the study and approved the final version.

Conflicts of Interest

The authors declare no conflict of interest.

Supplementary information is available at JPER's website.

Introduction

Retinopathy of prematurity (ROP) is a disorder of abnormal retinal vascular development occurring in preterm infants and is associated with long-term adverse visual outcomes. Incidence of severe ROP in very low birth weight infants is approximately 6%.[1] Significant visual impairment frequently occurs in children with severe ROP; for example, the Early Treatment for Retinopathy of Prematurity (ETROP) Study reported that 25% of infants with advanced ROP requiring treatment had severe visual impairment at 6 years of age.[2] Though treatment of severe cases with intravitreal anti-vascular endothelial growth factor (VEGF) and laser therapy improves outcomes, ultimately, the best method to decrease ROP-related morbidity is by preventing its progression to the severe stage. New prevention strategies are needed, and likely will stem from advances to our understanding of ROP's pathogenesis.

ROP is a multifactorial disease involving both prenatal and postnatal factors. The pathogenesis is thought to have two sequential phases.[3–5] The first phase involves relative hyperoxia leading to slowing or cessation of normal retinal vascularization, i.e. angiogenesis. Upon preterm birth, the immature retina is exposed to higher levels of oxygen, which leads to lower retinal growth factor levels, and consequently slowing of retinal blood vessel growth. The second phase of ROP pathogenesis is characterized by deleterious neovascularization in the setting of relative hypoxia. The lack of blood vessel growth in the retina in the first phase results in retinal ischemia, increased metabolic demand of the retina, upregulation of retinal growth factors (including VEGF), and ultimately, formation of new collateral blood vessels, i.e. neovascularization. Left untreated, neovascularization may cause retinal detachment and permanent vision loss. What is not well understood are the precise mechanisms underlying the progression from phase one to phase two of ROP pathogenesis, and the progression through phase two to retinal detachment.[6]

Notably, there is much to learn about the role of inflammation in ROP.[6] Recent studies suggest that prenatal and postnatal inflammation may each contribute to increased risk of ROP.[4,6–8] Inflammatory factors such as cytokines, chemokines, growth factors, leucocytes, monocytes, and macrophages are implicated in the control of angiogenesis and contribute to the developing vasculature in ROP.[6,9–13] Additionally, systemic inflammation may affect retinal angiogenesis by sensitizing the developing retina to oxygen-induced changes in growth factor availability and subsequent neovascularization.[4] Therefore, inflammation may both increase susceptibility to phase one and progression through phase two of ROP pathogenesis. Additionally, it has been shown that fetal exposure to inflammation increases risk of other common complications of prematurity, namely bronchopulmonary dysplasia and cerebral palsy.[14–17] Chronic biochemical chorioamnionitis can lead to fetal inflammatory response syndrome, producing a prenatal inflammatory exposure.[14] Studies assessing maternal and fetal inflammation-associated risk factors for ROP, such as chorioamnionitis and pre-eclampsia, have been inconclusive.[18–20] Studies assessing postnatal risk factors for ROP have identified a number of risk factors.[21,22] However, a recent review described some of the postnatal risk factor study results as contradictory, unreplicated, and/or limited by confounding with other known risk factors.[21] Furthermore, a 2016 American Academy of Ophthalmology report suggested that current ROP risk

prediction models cannot be widely used because of limited generalizability and small sample size.[23]

Based on this evidence, our hypothesis was that inflammation plays a central role in progression of ROP and that prenatal and postnatal exposure to inflammatory factors increases risk of severe ROP. Given the need to better quantify the risk associated with exposure to inflammatory risk factors before and after birth, we examined this association with a population-based cohort study.[21] A better understanding of the association between inflammatory risk factors and ROP will help tailor risk prediction, patient selection for screening exams, and advance our understanding of ROP pathogenesis, potentially leading to new treatments involving anti-inflammatory targets.

Methods

Study population:

This population-based cohort study used data collected by the California Perinatal Quality Care Collaborative (CPQCC), the California Office of Statewide Health Planning and Development (OSHPD), and the California Department of Public Health. The CPQCC is a quality improvement organization that collects data from 137 California hospital neonatal intensive care units (NICUs), representing over 90% of neonates cared for in California.[24] The CPQCC collects clinical data prospectively, using standard definitions developed by the Vermont Oxford Network.[25] The CPQCC assures high data quality through training of local personnel, range and logic checks, and auditing of records with excessive missing data. The CPQCC data are linked to birth certificates, infant death certificates, and OSHPD hospital discharge data from the delivery hospitalization as well as across multiple hospitals for infants transferred to other member NICUs. This study was approved by the Stanford University Institutional Review Board on Human Subjects Research and the State of California Committee for the Protection of Human Subjects.

Study design:

We examined all infants with data available from the CPQCC born from January 1st, 2007 to December 31st, 2011. We limited our analysis to patients who were born 22 weeks and 0 days' to 29 weeks and 6 days' gestational age. We chose < 30 weeks' gestation because the CPQCC did not collect data on all infants ≥ 30 weeks during our study period and this gestational age cut-off nearly matches the American Academy of Pediatricians (AAP) recommendation to screen all infants < 31 weeks' gestation with a retinal exam evaluating for ROP.[26] We further excluded patients with birth weights at the extremes for their gestational ages (i.e. <1st or >99th percentiles), those missing data for any variables included in the analyses, and infants still alive at discharge but without a screening ROP exam performed by an ophthalmologist. Infants who died prior to ROP exam were excluded from our primary analysis but were included in a sensitivity analysis.

Prenatal exposures:

Prenatal variables associated with a maternal or fetal pro-inflammatory state were chosen based on prior evidence.[27–33] These variables included pre-pregnancy maternal body mass

index (BMI), pre-pregnancy hypertension, type I or type II diabetes mellitus, prolonged rupture of membranes (ROM), preterm premature rupture of membranes (PPROM), preterm labor, chorioamnionitis, maternal autoimmune disease, and congenital infection. Pre-pregnancy BMI was calculated from maternal weight divided by height-squared reported on the birth certificate. BMI was divided into four categories: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2).[34] We did not examine gestational hypertension or gestational diabetes because, frequently, mothers of extremely preterm infants have yet to develop these conditions at the time of extremely preterm birth. Prolonged ROM was defined as rupture of the membranes more than 18 hours prior to birth of the infant. PPROM was defined as spontaneous rupture of membranes at a gestational age of less than 37 weeks. Preterm labor was defined as regular contractions in the context of cervical change that occurred at less than 37 weeks. Chorioamnionitis was defined by the maternal medical record giving evidence of infections of the amniotic sac and fluid (amnionitis) or those of the uterine wall (endometritis). Maternal autoimmune disease included any of the following conditions: autoimmune thyroiditis, psoriasis, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, or systemic lupus erythematosus. Congenital infection was defined as congenital toxoplasmosis, rubella virus, syphilis, cytomegalovirus, herpes simplex virus, parvovirus, zika virus or varicella zoster virus. Supplemental table 1 lists the data source for each exposure variable and associated *International Classification of Disease Clinical Modification 9th Revision* (ICD-9-CM) diagnosis codes.

The prenatal risk factors were combined into a single variable in order to assess mediation by gestational age of an association between prenatal inflammation exposure and ROP. We used logistic principal components analysis (‘logisticPCA’ package in R) to create the composite prenatal inflammation variable. Principal components analysis is a common technique to combine multiple related predictors. The first principal component was selected and retained because it captured the majority of the variance. This variable served as a marker of prenatal inflammation. Because the mediation analysis required a binary predictor and the variable was standardized with mean 0, we defined lower prenatal inflammation as ≤0 and higher prenatal inflammation as >0.

Postnatal exposures:

Postnatal variables associated with a neonatal pro-inflammatory state were limited to conditions that most often occur prior to development of severe ROP necessitating treatment, which has a peak incidence of 35–40 weeks’ postmenstrual gestational age in preterm infants.[35] Postnatal inflammatory-related variables included supplemental oxygen use on day of life 28 (a proxy for both hyperoxia and future diagnosis of bronchopulmonary dysplasia), early bacterial sepsis, late-onset sepsis, intraventricular hemorrhage (IVH) grades 3 or 4, and necrotizing enterocolitis (NEC). Early bacterial sepsis was defined as a bacterial pathogen recovered from a blood and/or cerebrospinal fluid culture obtained on day 1, 2 or 3 of life. Late-onset sepsis was defined as bacteria recovered from a blood and/or cerebrospinal fluid culture after day 3 of life and prior to initial disposition or after readmission. Late-onset sepsis may occur before or after ROP development. IVH was defined as the worst grade obtained on cranial ultrasound, computed tomography scan or

magnetic resonance imaging performed on or before day of life 28. Grade 3 IVH is defined as intraventricular blood with ventricular dilation. Grade 4 IVH is defined as intraparenchymal hemorrhage. In most cases, IVH occurs in the first week of life, prior to ROP development.[36] NEC was diagnosed at surgery, at postmortem examination or clinically and radiographically using the following criteria: at least one of the following clinical signs present: 1) bilious gastric aspirate or emesis, 2) abdominal distension, 3) occult or gross blood in stool (no fissure) AND at least one of the following radiographic findings present: 1) pneumatosis intestinalis, 2) hepato-biliary gas, 3) pneumoperitoneum. This definition for NEC also requires that infants with spontaneous intestinal perforation confirmed at laparotomy or post-mortem examination be excluded. NEC incidence peaks at 30–32 weeks postmenstrual age, which is most often prior to development of severe ROP.[37]

Covariates:

Other variables of interest were maternal race/ethnicity, age, and education, expected method of payment for delivery, infant sex, birthweight, and gestational age at delivery. These variables were selected *a priori* for inclusion in the multivariable models as confounding variables based on prior knowledge, causal diagrams, and available data.[21,22]

Outcome:

ROP was categorized as “severe” if disease was graded as stage 3, 4 or 5 or if disease necessitated treatment with laser surgery or cryosurgery. Of note, the CPQCC did not collect data on anti-VEGF treatment or plus disease (i.e. engorged or tortuous blood vessels, which substantially increases risk of retinal detachment) during the study years we examined, and therefore we could not use either as an outcome. ROP screening is recommended by the AAP for all infants ≤ 30 weeks’ gestational age, infants ≤ 1500 grams, or other select infants with an unstable clinical course believed to be high risk for ROP by their attending provider.[26] Retinal examination screening generally begins at 31 weeks’ postmenstrual gestational age or at 4 weeks chronologic age for infants born at or later than 28 weeks’ gestational age.[26] Peak timing of onset of severe ROP necessitating treatment is 35 to 40 weeks postmenstrual age.[35] Stage 1 ROP is defined on retinal examination by a demarcation line between the vascular and avascular areas of the retina. Stage 2 ROP is defined by the presence of a ridge arising from the demarcation line. Stage 3 ROP represents the presence of a ridge with extraretinal fibrovascular proliferation. Stage 4 ROP represents partial retinal detachment. Stage 5 ROP represents total retinal detachment. Death before ROP examination is a competing outcome, which we assessed in a sensitivity analysis.

Statistical analysis:

Patient characteristics were first characterized by outcome status. Separate log-binomial regression models were used to estimate risk ratios with 95% confidence intervals for associations of each prenatal inflammatory risk factor with ROP. Each model adjusted for maternal age at delivery, race/ethnicity, education, expected method of payment for delivery, and infant sex. Estimates were considered statistically significant at $P < 0.05$. A marginal structural modeling approach was then used to assess mediation of an association between prenatal inflammation and ROP by gestational age at birth.[38] To do so, a multivariable linear regression model was fit with gestational age as the outcome, the composite prenatal

inflammation variable as the predictor, and confounders adjusted. A counterfactual dataset was then made by replicating the actual dataset and setting prenatal inflammation to the opposite of its actual value. Inverse probability weights were computed by applying the fitted models to the actual and counterfactual datasets. A multivariable log-binomial regression model for the outcome, ROP, was then fit with generalized estimating equations to obtain estimates of the natural direct effect (NDE) and natural indirect effect (NIE) of prenatal inflammation on ROP with mediation by gestational age. The NDE is what the effect of prenatal inflammation on ROP would be if we disabled the pathway from prenatal inflammation to gestational age. The NIE is the effect of gestational age on ROP if prenatal inflammation were fixed. An interaction term between prenatal inflammation and gestational age was also tested in the regression model. The proportion of the association between prenatal inflammation and ROP mediated by gestational age was calculated using the following equation (RR = relative risk):[39]

$$\frac{RR^{NDE}(RR^{NIE}-1)}{(RR^{NDE}\times RR^{NIE}-1)}$$

Postnatal inflammatory risk factors for ROP were assessed in log-binomial regression models as described above for prenatal inflammatory risk factors, except gestational age at birth, which was included in the models as a confounder, not a mediator, because it precedes postnatal inflammation. For analyses of both prenatal and postnatal risk factors, we performed sensitivity analyses with postnatal death before ROP examination as a separate outcome. Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC) and R 3.4.4 (R Core Team, Vienna, Austria).[40]

Results

A total of 14,816 infants were included in the analysis after application of exclusion criteria (Figure 1). In this cohort, 10.8% of infants developed stage 3–5 ROP or required surgical treatment for ROP. Stage 4 or 5 ROP occurred in 0.33% of infants. Gestational age at birth differed significantly between infants with (i.e. cases) and without (i.e. controls) severe ROP (P<0.001) (Table 1). Mean gestational age at birth was 25.0 weeks for the infants with severe ROP and 27.2 weeks for the infants without severe ROP. There was also a significant difference in the racial/ethnic characteristics (P<0.001) between the case and control groups. Hispanic and Asian/Pacific Islander were represented more, while non-Hispanic black and white were represented less, in infants with severe ROP compared with infants without severe ROP.

Prenatal Inflammatory Factors and Severe ROP

With adjustment for covariates, though not yet including gestational age, prenatal inflammatory risk factors significantly associated with severe ROP were prolonged ROM (RR 1.18, 95% CI 1.05–1.33), PPROM or preterm labor (RR 1.35, 95% CI 1.10–1.65), chorioamnionitis (RR 1.33, 95% CI 1.13–1.56), and congenital infection (RR 1.88, 95% CI 1.21–2.92) (Table 2). Pre-pregnancy BMI, pre-pregnancy hypertension, diabetes mellitus

types I and II and autoimmune disease were not significant independent risk factors (i.e. confidence intervals crossed 1.0).

After creating a composite variable of prenatal inflammation, we found that higher prenatal inflammation was experienced by 31.6% of infants with severe ROP and 27.9% of infants without severe ROP. The confounder-adjusted risk of ROP in infants with higher prenatal inflammation was 1.18 times (95% CI 1.06–1.31) the risk in infants with lower prenatal inflammation (the total effect) (Figure 2). After accounting for the effect of prenatal inflammation on gestational age at birth via mediation analysis, the risk ratio was reduced to 1.03 (95% CI 0.93–1.13) (the natural direct effect). This finding indicates that lower gestational age among infants with higher prenatal inflammation than among unexposed infants explained most (84%) of the association between prenatal inflammation and ROP. There was no evidence for interaction between prenatal inflammation and gestational age ($P>0.1$). Additionally, we repeated the mediation test for individual prenatal conditions as a sensitivity analysis and the direct effects were not statistically significant.

The model from table 2 was re-examined with postnatal death before ROP examination as a combined outcome with severe ROP (Supplemental Table 2). Pre-pregnancy hypertension shows a protective effect on severe ROP or death, with RR 0.84 (95% CI 0.74–0.94). Prolonged ROM and congenital infection were not risk factors for severe ROP in this model (confidence intervals include 1.0), while PPROM or preterm labor, and chorioamnionitis were statistically significant risk factors.

Postnatal Inflammatory Factors and Severe ROP

With adjustment for covariates, including gestational age, postnatal risk factors associated with severe ROP included supplemental oxygen use at 28 days of life (RR 3.3, 95% CI 2.7–4.1), late-onset sepsis (RR 1.39, 95% CI 1.26–1.53), IVH grades 3–4 (RR 1.22, 95% CI 1.08–1.37), and NEC (RR 1.36, 95% CI 1.19–1.55). Early-onset bacterial sepsis was not significantly associated with severe ROP.

Discussion

Our results suggest that certain inflammation-related risk factors contribute to severe ROP development among early preterm infants. Prenatal inflammation-related risk factors were associated with severe ROP. However, this association became non-significant after accounting for the effect of gestational age as a mediating variable. Several postnatal inflammation-related risk factors, including prolonged oxygen use, necrotizing enterocolitis, late-onset sepsis and severe intraventricular hemorrhage were also associated with increased risk of severe ROP.

Our finding that prenatal risk factors associated with inflammation may have minimal contribution to severe ROP development supports prior evidence.[41] Villamor-Martinez et al. performed a meta-analysis of chorioamnionitis as a risk factor for ROP.[41] The authors found that chorioamnionitis was a risk factor for severe ROP, but after controlling for gestational age as a confounding variable, the association was non-significant. Here, we show similar

results by instead accounting for gestational age as a mediating variable, and with larger sample sizes than prior studies.

Biological evidence supports our findings that postnatal inflammation-related risk factors have a more prominent role in ROP development than prenatal inflammation-related risk factors. Extreme prematurity and relative hyperoxia exposure establish cessation of normal retinal blood vessel growth, representing phase 1 of ROP development. Prenatal inflammatory exposures may sensitize the infant to developing ROP, but these exposures would occur prior to phase 1, limiting their degree of impact. In contrast, postnatal inflammation-related exposures impact ROP development closer to the temporal timing of phase 1 and 2 of ROP pathogenesis. Our results indicate that several postnatal diseases related to prematurity, with a common theme of exaggerated release of inflammatory mediators, are each associated with increased risk of severe ROP. These conditions included evolving BPD, NEC, severe IVH and late-onset sepsis. These observational findings, in conjunction with prior evidence, suggest that inflammation plays a critical role in ROP development. The next questions to answer are what specific common inflammatory factors are involved in ROP pathogenesis, what are the mechanisms, and ultimately how can we target these mechanisms to prevent severe ROP.

Strengths of our study include its unusually large sample size, high quality data and rigorous methodology. We utilized a population-based data set that includes 1,600 infants with severe ROP. Additionally, the CPQCC database contains over 90% of preterm infants in California. Given that one in eight U.S. births occur in California, this suggests good generalizability of our results to other preterm infants across the U.S. Our study utilized methodology not typically used in prior studies assessing associations between prenatal risk factors and ROP. Because gestational age is on the causal path from prenatal exposures to ROP, it is a mediating or intermediate variable, rather than a confounding variable. Including gestational age as a confounder in regression models can lead to biased results.[42] Therefore, in our analysis of prenatal risk factors and ROP risk, we performed a principal components analysis and accounted for the effect of gestational age as a mediating variable. For associations between postnatal risk factors and ROP, gestational age is a confounding variable and should be adjusted for in regression models because it precedes the occurrence of the postnatal factors and is related to both the exposure and the outcome. For example, being born at an early gestational age increases the likelihood of oxygen administration and also confers an increased risk of ROP, thus serving as a confounder.

This study has several limitations. Although the risk factors identified should be considered as being associated with severe ROP, the observational design of our study makes causality uncertain. In particular, data were not available on several likely confounders, including partial pressure of oxygen fluctuations, duration of total parenteral nutrition, and NICUs may have had different policies for oxygen targets and alarms.[43,44] Of note, our NEC cases may inadvertently include some spontaneous intestinal perforation cases, with the latter likely representing less systemic inflammatory exposure than NEC. However, this misclassification would likely bias the relative risk towards the null, making our finding of an increased relative risk for NEC and severe ROP still valid.

Additionally, the risk factors in our analyses were proxies for inflammation, and not specific inflammatory mediators themselves. There are likely numerous inflammatory factors and mechanisms by which inflammation impacts ROP development, and we were limited to examining a relatively narrow and non-specific set of factors. We found that prenatal inflammation-related risk factors assessed in our study did not have a significant association with severe ROP. However, there may be a relationship between maternal and/or fetal inflammation and ROP that was not captured by the risk factors we examined. Furthermore, the risk factors in our analyses may exert influences on ROP development through mechanisms besides inflammation, but we were unable to confirm this with the available data. Additionally, we acknowledge that we were unable to confirm the extent to which the markers of inflammation that we examined actually manifested inflammatory stimuli. We believe this limitation is of greatest concern for prenatal maternal conditions. Finally, we were limited by lack of more specific ROP data. Ophthalmologists use retinal exam findings in addition to ROP stage to assess severity and need for treatment. This includes the presence of plus disease, location of the plus disease, and the degree of retinal vessel immaturity (i.e the zone). If these data were available we could have assessed whether inflammation-related risk factors impact subtypes of severe ROP differently, such as those with plus disease.

In summary, we found that neonatal morbidities associated with extreme prematurity, including evolving bronchopulmonary dysplasia, necrotizing enterocolitis, severe intraventricular hemorrhage and late-onset sepsis, are associated with an increased risk of severe ROP. We also found that prenatal inflammation-related risk factors, including obesity, pre-gestational hypertension, type I and II diabetes mellitus, preterm labor, prolonged rupture of membranes, preterm premature rupture of membranes, chorioamnionitis, autoimmune disease and congenital infection have little to no direct measurable impact on risk of severe ROP; rather, their association with severe ROP is explained by the mediating effect of earlier gestational age. We theorize that postnatal inflammatory risk factors affect ROP development by accelerating the process of intravitreal neovascularization. Further research is needed to better understand the mechanisms surrounding how inflammation affects intravitreal neovascularization and how these mechanisms may lead to new therapeutic preventative strategies to reduce severe ROP incidence and morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Horbar JD, Edwards EM, Greenberg LT, Morrow KA, Soll RF, Buus-Frank ME et al. Variation in Performance of Neonatal Intensive Care Units in the United States. JAMA Pediatr 2017; 171: e164396. [PubMed: 28068438]
2. Early Treatment for Retinopathy of Prematurity Cooperative Group, Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL et al. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol Chic Ill 1960 2010; 128: 663–671.
3. Chen J, Smith LEH. Retinopathy of prematurity. Angiogenesis 2007; 10: 133–140. [PubMed: 17332988]
4. Lee J, Dammann O. Perinatal infection, inflammation, and retinopathy of prematurity. Semin Fetal Neonatal Med 2012; 17: 26–29. [PubMed: 21903492]
5. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. N Engl J Med 2012; 367: 2515–2526. [PubMed: 23268666]
6. Rivera JC, Holm M, Austeng D, Morken TS, Zhou TE, Beaudry-Richard A et al. Retinopathy of prematurity: inflammation, choroidal degeneration, and novel promising therapeutic strategies. J Neuroinflammation 2017; 14: 165. [PubMed: 28830469]
7. Lynch AM, Berning AA, Thevarajah TS, Wagner BD, Post MD, McCourt EA et al. The role of the maternal and fetal inflammatory response in retinopathy of prematurity. Am J Reprod Immunol N Y N 1989 2018; : e12986.
8. Beaudry-Richard A, Nadeau-Vallée M, Prairie É, Maurice N, Heckel É, Nezhady M et al. Antenatal IL-1-dependent inflammation persists postnatally and causes retinal and sub-retinal vasculopathy in progeny. Sci Rep 2018; 8: 11875. [PubMed: 30089839]
9. Szade A, Grochot-Przeczek A, Florczyk U, Jozkowicz A, Dulak J. Cellular and molecular mechanisms of inflammation-induced angiogenesis. IUBMB Life 2015; 67: 145–159. [PubMed: 25899846]
10. Yu H, Yuan L, Zou Y, Peng L, Wang Y, Li T et al. Serum concentrations of cytokines in infants with retinopathy of prematurity. APMIS Acta Pathol Microbiol Immunol Scand 2014; 122: 818–823.
11. Gardiner TA, Gibson DS, de Gooyer TE, de la Cruz VF, McDonald DM, Stitt AW. Inhibition of tumor necrosis factor-alpha improves physiological angiogenesis and reduces pathological neovascularization in ischemic retinopathy. Am J Pathol 2005; 166: 637–644. [PubMed: 15681845]
12. Hong HK, Lee HJ, Ko JH, Park JH, Park JY, Choi CW et al. Neonatal systemic inflammation in rats alters retinal vessel development and simulates pathologic features of retinopathy of prematurity. J Neuroinflammation 2014; 11: 87. [PubMed: 24886524]
13. Tremblay S, Miloudi K, Chaychi S, Favret S, Binet F, Polosa A et al. Systemic inflammation perturbs developmental retinal angiogenesis and neuroretinal function. Invest Ophthalmol Vis Sci 2013; 54: 8125–8139. [PubMed: 24204040]
14. Thomas W, Speer CP. Chorioamnionitis: important risk factor or innocent bystander for neonatal outcome? Neonatology 2011; 99: 177–187. [PubMed: 20881433]
15. Combs CA, Gravett M, Garite TJ, Hickok DE, Lapidus J, Porreco R et al. Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. Am J Obstet Gynecol 2014; 210: 125.e1–125.e15. [PubMed: 24274987]
16. Yoon BH, Romero R, Park JS, Kim CJ, Kim SH, Choi JH et al. Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol 2000; 182: 675–681. [PubMed: 10739529]
17. Nelson KB, Dambrosia JM, Grether JK, Phillips TM. Neonatal cytokines and coagulation factors in children with cerebral palsy. Ann Neurol 1998; 44: 665–675. [PubMed: 9778266]
18. Fortes Filho JB, Costa MC, Eckert GU, Santos PGB, Silveira RC, Procianoy RS. Maternal preeclampsia protects preterm infants against severe retinopathy of prematurity. J Pediatr 2011; 158: 372–376. [PubMed: 20888573]

19. Hendson L, Russell L, Robertson CMT, Liang Y, Chen Y, Abdalla A et al. Neonatal and neurodevelopmental outcomes of very low birth weight infants with histologic chorioamnionitis. J Pediatr 2011; 158: 397–402. [PubMed: 20961565]
20. Mitra S, Aune D, Speer CP, Saugstad OD. Chorioamnionitis as a risk factor for retinopathy of prematurity: a systematic review and meta-analysis. Neonatology 2014; 105: 189–199. [PubMed: 24481268]
21. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Surv Ophthalmol 2018; 63: 618–637. [PubMed: 29679617]
22. Slidsborg C, Jensen A, Forman JL, Rasmussen S, Bangsgaard R, Fledelius HC et al. Neonatal Risk Factors for Treatment-Demanding Retinopathy of Prematurity: A Danish National Study. Ophthalmology 2016; 123: 796–803. [PubMed: 26854038]
23. Hutchinson AK, Melia M, Yang MB, VanderVeen DK, Wilson LB, Lambert SR. Clinical Models and Algorithms for the Prediction of Retinopathy of Prematurity: A Report by the American Academy of Ophthalmology. Ophthalmology 2016; 123: 804–816. [PubMed: 26832657]
24. California Perinatal Quality Care Collaborative |. https://www.cpqcc.org/.
25. Vermont Oxford Network – Improving care for infants and their families. https://public.vtoxford.org/.
26. Fierson WM, American Academy of Pediatric Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening Examination of Premature Infants for Retinopathy of Prematurity. Pediatrics 2018. doi:10.1542/peds.2018-3061.
27. Segovia SA, Vickers MH, Reynolds CM. The impact of maternal obesity on inflammatory processes and consequences for later offspring health outcomes. J Dev Orig Health Dis 2017; 8: 529–540. [PubMed: 28343461]
28. Kim SM, Romero R, Park JW, Oh KJ, Jun JK, Yoon BH. The relationship between the intensity of intra-amniotic inflammation and the presence and severity of acute histologic chorioamnionitis in preterm gestation. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet 2015; 28: 1500–1509.
29. Boisen AB, Knorr S, Hansen TK, Vlachova Z, Bytoft B, Damm P et al. Signs of low-grade systemic inflammation in female offspring of women with type 1 diabetes: The EPICOM study. Diabetes Metab 2016; 42: 462–465. [PubMed: 27378631]
30. Sharma K, Singh R, Kumar M, Gupta U, Rohil V, Bhattacharjee J. First-Trimester Inflammatory Markers for Risk Evaluation of Pregnancy Hypertension. J Obstet Gynaecol India 2018; 68: 27–32. [PubMed: 29391672]
31. Kalagiri RR, Carder T, Choudhury S, Vora N, Ballard AR, Govande V et al. Inflammation in Complicated Pregnancy and Its Outcome. Am J Perinatol 2016; 33: 1337–1356. [PubMed: 27159203]
32. Musilova I, Andrys C, Drahosova M, Soucek O, Stepan M, Bestvina T et al. Intraamniotic inflammation and umbilical cord blood interleukin-6 concentrations in pregnancies complicated by preterm prelabor rupture of membranes. J Matern Fetal Neonatal Med 2017; 30: 900–910. [PubMed: 27265200]
33. Cardenas I, Means RE, Aldo P, Koga K, Lang SM, Booth CJ et al. Viral infection of the placenta leads to fetal inflammation and sensitization to bacterial products predisposing to preterm labor. J Immunol 2010; 185: 1248–1257. [PubMed: 20554966]
34. WHO:: Global Database on Body Mass Index. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.
35. Kennedy KA, Wrage LA, Higgins RD, Finer NN, Carlo WA, Walsh MC et al. Evaluating retinopathy of prematurity screening guidelines for 24- to 27-week gestational age infants. J Perinatol Off J Calif Perinat Assoc 2014; 34: 311–318.
36. Al-Abdi SY, Al-Aamri MA. A Systematic Review and Meta-analysis of the Timing of Early Intraventricular Hemorrhage in Preterm Neonates: Clinical and Research Implications. J Clin Neonatol 2014; 3: 76–88. [PubMed: 25024973]

37. Yee WH, Soraisham AS, Shah VS, Aziz K, Yoon W, Lee SK et al. Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. Pediatrics 2012; 129: e298–304. [PubMed: 22271701]

38. Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. Am J Epidemiol 2012; 176: 190–195. [PubMed: 22781427]

39. Vanderweele TJ. Explanation in causal inference: Methods for mediation and interaction. Oxford University Press: New York, NY, US, 2015.

40. R: The R Project for Statistical Computing. https://www.r-project.org/.

41. Villamor-Martinez E, Cavallaro G, Raffaeli G, Mohammed Rahim OMM, Gulden S, Ghazi AMT et al. Chorioamnionitis as a risk factor for retinopathy of prematurity: An updated systematic review and meta-analysis. PloS One 2018; 13: e0205838. [PubMed: 30332485]

42. Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. Am J Epidemiol 2011; 174: 1062–1068. [PubMed: 21946386]

43. York JR, Landers S, Kirby RS, Arbogast PG, Penn JS. Arterial oxygen fluctuation and retinopathy of prematurity in very-low-birth-weight infants. J Perinatol Off J Calif Perinat Assoc 2004; 24: 82–87.

44. Wu C, Löfqvist C, Smith LEH, VanderVeen DK, Hellström A, WINROP Consortium. Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants: a multicenter study analyzing weight velocity deviations for the prediction of retinopathy of prematurity. Arch Ophthalmol Chic Ill 1960 2012; 130: 992–999.

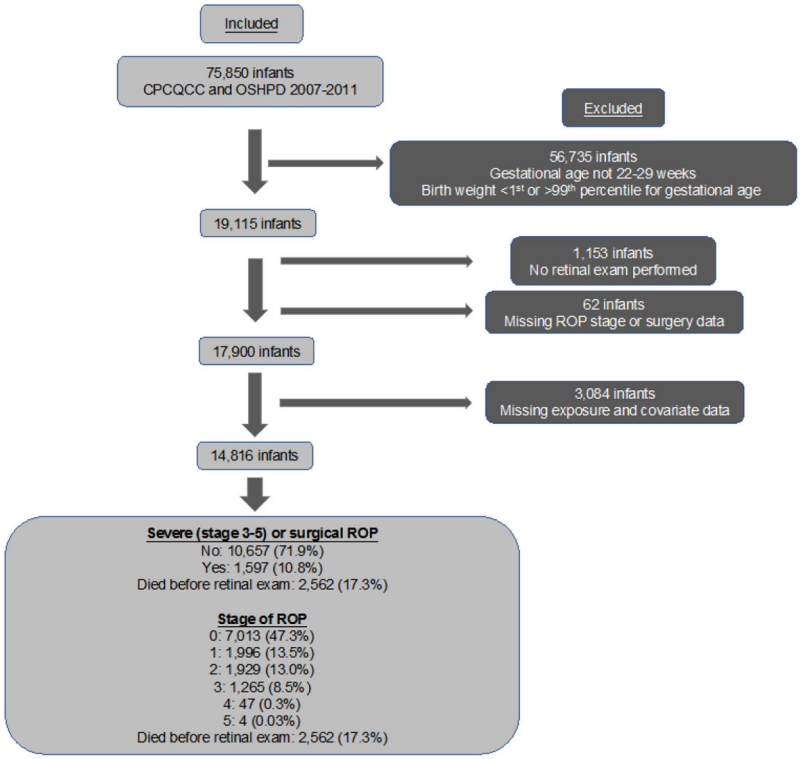

Figure 1.
Patients included in the study after inclusion and exclusion criteria, and listed by stage of ROP.

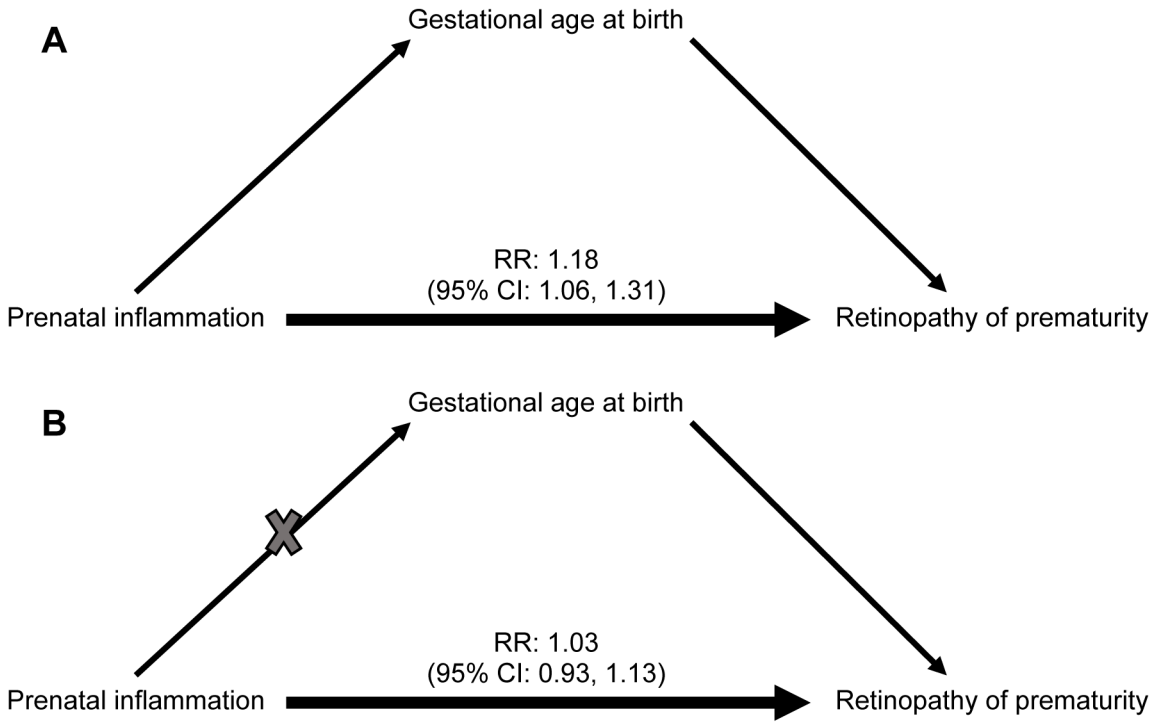

Figure 2.

Diagrams of estimates of total effects of prenatal inflammation on risk of retinopathy of prematurity (A), and natural direct effect for mediation by gestational age at birth (B). Risk ratio (RR) and 95% confidence interval (CI) shown correspond to each emboldened pathway.

Table 1.

Baseline patient characteristics of infants with and without severe ROP in California, 2007-2011.

Variable	No/Mild ROP (n = 12,575) n (%)	Severe ROP (n = 1,869) n (%)
Mother		
Age (years), mean (SD[1])	28.9 (7)	28.6 (6.9)
Education		
Less than high school	2,920 (23.2)	441 (23.6)
High school degree or equivalent	3,091 (24.6)	506 (27.1)
Some college	2,326 (18.5)	326 (17.4)
Associate degree	591 (4.7)	114 (6.1)
Undergraduate degree	1,665 (13.2)	244 (13.1)
Postgraduate degree	879 (7.0)	102 (5.5)
Unknown	1,103 (8.8)	136 (7.3)
Expected method of payment for delivery		
Medi-Cal	5,729 (45.6)	846 (45.3)
Private insurance	5,294 (42.1)	786 (42.1)
Uninsured	545 (4.3)	85 (4.5)
Other/Unknown	1,007 (8.0)	152 (8.1)
Race/ethnicity		
Non-Hispanic black	1,775 (14.0)	219 (11.7)
Hispanic/Latina	5,918 (47.1)	959 (51.3)
Non-Hispanic white	3,380 (26.9)	434 (23.2)
Asian/Pacific Islander	1,203 (9.6)	211 (11.3)
Other	319 (2.5)	46 (2.5)
Infant		
Birth weight (grams), mean (SD)	1039 (268)	740 (173)
Gestational age at birth		
22 weeks	16 (0.1)	30 (1.6)
23 weeks	234 (1.9)	212 (11.3)
24 weeks	716 (5.7)	522 (27.9)
25 weeks	1,174 (9.3)	534 (28.6)
26 weeks	1,768 (14.1)	302 (16.2)
27 weeks	2,305 (18.3)	158 (8.5)
28 weeks	2,911 (23.1)	72 (3.9)
29 weeks	3,451 (27.4)	39 (2.1)
Sex		
Female	5,883 (46.8)	847 (45.3)
Male	6,688 (53.2)	1,022 (54.7)

[1]Standard deviation

Table 2.

Associations between prenatal inflammation-related risk factors and severe retinopathy of prematurity.

Risk Factor	No/Mild ROP (n = 10,657) n (%)	Severe ROP (n = 1,597) n (%)	Risk Ratio[1] (95% CI[2])
Chorioamnionitis	809 (7.6)	162 (10.1)	1.33 (1.13-1.56)
Congenital infection	61 (0.6)	20 (1.3)	1.88 (1.21-2.92)
Diabetes mellitus type I or II	327 (3.1)	54 (3.4)	1.11 (0.85-1.46)
Maternal autoimmune disease[3]	96 (0.9)	9 (1.2)	1.26 (0.80-1.99)
Pre-pregnancy BMI (kg/m^2)[4]			
Underweight	415 (3.9)	58 (3.6)	0.94 (0.72-1.23)
Normal weight	4,579 (43.0)	659 (41.3)	Reference
Overweight	2,783 (26.1)	440 (27.6)	1.09 (0.96-1.23)
Obesity	2,880 (27.0)	440 (27.6)	1.07 (0.94-1.21)
Pre-pregnancy hypertension	917 (8.6)	138 (8.6)	1.04 (0.87-1.24)
Preterm labor or PPROM[5]			
Both	2,519 (23.6)	436 (27.3)	1.35 (1.10-1.65)
PPROM only	461 (4.3)	66 (4.1)	1.15 (0.85-1.55)
Preterm labor only	6,662 (62.5)	972 (60.9)	1.15 (0.95-1.39)
Neither	1,015 (9.5)	123 (7.7)	Reference
Prolonged ROM[6]	2.007 (18.8)	342 (21.4)	1.18 (1.05-1.33)

[1] Separate models were run for each risk factor in the table. Each model was adjusted for maternal age, race/ethnicity, education, expected payment method, and infant sex.

[2] Confidence interval

[3] Autoimmune disease included maternal autoimmune thyroiditis, maternal psoriasis, maternal multiple sclerosis, maternal inflammatory bowel disease, maternal rheumatoid arthritis, maternal systemic lupus erythematosus.

[4] Underweight = BMI <18.5; normal weight = BMI 18.5-24.9; overweight = BMI 25-29.9; obesity = BMI ≥30

[5] Preterm premature rupture of membranes

[6] Rupture of membranes

Table 3.

Associations between postnatal inflammation-related risk factors and severe retinopathy of prematurity.

Risk Factor	No/Mild ROP (n = 10,657) n (%)	Severe ROP (n = 1,597) n (%)	Risk Ratio[1] (95% CI)
Early bacterial sepsis	210 (1.7)	51 (2.7)	1.00 (0.76-1.32)
Late-onset sepsis	2,300 (18.3)	752 (40.2)	1.39 (1.26-1.53)
Necrotizing enterocolitis	802 (6.4)	276 (14.8)	1.36 (1.19-1.55)
Severe intraventricular hemorrhage[2]	885 (7.0)	327 (17.5)	1.22 (1.08-1.37)
Supplemental oxygen on day 28	674 (61.1)	1,774 (94.9)	3.30 (2.66-4.10)

[1] Separate models were run for each risk factor in the table. Each model was adjusted for maternal age, race/ethnicity, education, expected payment method, infant sex, and gestational age.

[2] Grades 3-4.