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Retinopathy of Prematurity in Substance-Exposed Premature Infants: A Retrospective Cohort Analysis Using the TriNetX Research Network

Tammy Corr

tcorr@pennstatehealth.psu.edu

Penn State College of Medicine https://orcid.org/0000-0003-4169-7396

Shivani Bhargava

Ananya Sridharan

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Abstract

Objective

Determine whether prenatal substance exposure is associated with an increased incidence of retinopathy of prematurity (ROP).

Design:

Retrospective cohort study using the TriNetX Research Network. Infants born ≤ 30 weeks' gestation and/or < 1500 grams were divided into substance-exposed (n = 750) and non-exposed cohorts (n = 34,961) using ICD-10 codes. ROP diagnoses were captured using stage-specific ICD-10 subcodes.

Results

ROP was more common in substance-exposed infants (82.7% vs 69.5%; OR 2.09, 95% CI 1.73–2.53). Substance-exposed infants had higher rates of stage 1 (36.0% vs 21.7%), stage 2 (25.2% vs 16.4%), stage 3 (14.3% vs 9.8%), and stage 4 ROP (1.3% vs 0.5%; all $p < 0.001$). Distributions of prematurity and birth weight were similar between cohorts.

Conclusion

Prenatal substance exposure was associated with significantly higher odds of ROP stages 1–4, suggesting it may be an independent risk factor for ROP development and severity, with potential implications for neonatal screening practices.

Introduction

Retinopathy of prematurity (ROP) arises when the normal, sequential development of retinal blood vessels is interrupted by premature birth, exposing an incompletely vascularized retina to a postnatal environment for which it is not yet prepared. In infants born below 1500 grams, reported ROP incidence is approximately 40%, and rates climb further as gestational age and birth weight decrease. [1] Large cohort studies illustrate this gradient clearly: one series found that while the overall incidence of any-stage ROP was 43.5%, this rate rose to 81.1% among infants weighing 1000 grams or less at birth and to 92.9% among those born at or before 25 weeks' gestation. [2]

The pathophysiology of ROP is classically described in two phases. In the first phase, relative hyperoxia following delivery suppresses vascular endothelial growth factor (VEGF) signaling and halts normal retinal vessel growth. As the retina matures and its metabolic demands increase, the resulting relative hypoxia in the second phase triggers a compensatory, but pathological, surge of VEGF-driven

neovascularization, which can progress to fibrovascular proliferation, tractional retinal detachment, and, if untreated, blindness. [3] Extensive literature has identified several risk factors that modulate this process, including prolonged supplemental oxygen or mechanical ventilation, intraventricular hemorrhage, sepsis, bronchopulmonary dysplasia, and need for blood transfusion, but decreasing gestational age and birth weight continue to confer the greatest risk. [4]

Prematurity is disproportionately present among substance-exposed neonates, and prenatal substance exposure remains a common complication of pregnancy in the United States. National surveillance data show that the incidence of neonatal abstinence syndrome (NAS) rose nearly 300% between 1999 and 2013, from 1.5 to 6.0 cases per 1 000 hospital births, with continued increases through the mid-2010s before recent regional plateaus. [5,6] More recent Medicaid-based estimates indicate that broader prenatal substance exposure, encompassing opioids, cocaine, cannabis, and other illicit substances, has continued to rise even in states where NAS diagnoses specifically have leveled off, suggesting that the population of substance-exposed newborns is both substantial and growing. [7]

Because substance-exposed pregnancies are more likely to result in preterm birth, there is considerable overlap between infants exposed to substances prenatally and those already at highest risk for ROP. However, it remains unclear whether, among infants of comparable gestational age and birth weight, prenatal substance exposure itself confers additional risk for ROP development or severity. Therefore, the present study is designed to address this gap. We hypothesized that infants with prenatal substance exposure would demonstrate a higher incidence of ROP compared with non-exposed infants of similar gestational age and birth weight.

Methods

This retrospective cohort study used deidentified, aggregated electronic health record data from the TriNetX Research Network, a federated real-world data platform drawing on records of more than 150 million patients from participating healthcare organizations worldwide. [8]

Study Population

Utilizing the TriNetX network, a cohort of premature infants born at ≤ 30 weeks' gestation and/or < 1500 grams at birth were identified using the International Classification of Diseases, 10th Revision (ICD-10) codes P07.00-P07.03 (extremely low birth weight newborn), P07.10-P07.15 (other low birth weight newborn), P07.20-P07.26 (extreme immaturity), and P07.30-P07.33 (preterm newborn). Substance-exposed infants were then identified using the ICD-10 codes P04.4 (newborn affected by maternal use of drugs of addiction), P04.14 (newborn affected by maternal use of opiates), P96.1 (neonatal withdrawal symptoms from maternal use of drugs of addiction), and P04.49 (newborn affected by other maternal use of drugs of addiction). Infants were divided into substance-exposed and substance non-exposed cohorts based on the presence or absence of these ICD-10-coded definitions.

Outcome Definitions

ROP disease severity is classified using the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3), which standardizes staging by zone, stage, extent, and the presence of plus disease. [9] Thus, the primary outcome of this study was diagnosis of ROP and stage of disease, which were captured using ICD-10 code H35.1 (retinopathy of prematurity) and the related stage-specific subcodes (H35.10-H35.16)

Statistical Analysis

Comparability of the two cohorts with respect to degree of prematurity was assessed using the distribution of ICD-10 P07 codes (disorders related to short gestation and low birth weight), which capture both birth weight category (e.g., P07.0, extremely low birth weight; P07.1, other low birth weight) and gestational age category (e.g., P07.2, extreme immaturity; P07.3, other preterm birth) at the level of individual weight bands and completed weeks of gestation.

Differences in outcome prevalence between the substance-exposed and non-exposed cohorts were assessed using a two-sample *z*-test for independent proportions. Two-sided *p*-values were calculated, and statistical significance was defined as $p < 0.05$. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to quantify the association between prenatal substance exposure and retinopathy of prematurity (ROP).

Results

A total of 750 infants met inclusion criteria for the substance-exposed cohort and 34,961 infants met criteria for the substance non-exposed comparison cohort. There were slightly more males than females in both cohorts, and the most infants were classified as non-Hispanic white (Table 1).

Table 1
Infant Demographic Characteristics

Characteristic	Substance Non-Exposed (N = 34 961)	Substance-Exposed (N = 750)
Sex, n (%)		
Male	18 253 (52.2%)	407 (54.3%)
Female	16 701 (47.8%)	342 (45.6%)
Unknown	10 (0.03%)	10 (1.4%)
Ethnicity, n (%)		
Not Hispanic or Latino	20 459 (58.5%)	441 (58.9%)
Hispanic or Latino	6 258 (17.9%)	89 (11.9%)
Unknown	8 244 (23.6%)	220 (29.3%)
Race, n (%)		
White	16 694 (47.8%)	389 (51.9%)
Black or African American	9 457 (27.1%)	227 (30.3%)
Asian	1 122 (3.2%)	10 (1.4%)
American Indian or Alaska Native	245 (0.70%)	10 (1.4%)
Native Hawaiian or Other Pacific Islander	182 (0.52%)	10 (1.4%)
Other	2 486 (7.1%)	41 (5.4%)
Unknown	4 776 (13.7%)	83 (11.0%)

As expected, the majority of infants had birth weights of < 1500 grams given the inclusion criteria, though there were some infants with weights > 1500 grams whose gestational age met qualifying study criteria and vice versa (infant gestational age was > 30 weeks but birth weight was < 1500 grams) (Table 2).

Table 2
Prematurity and Birth Weight Distributions1

ICD-10[2] Code	Description	Substance Non-Exposed (N = 34 961)	Substance-Exposed (N = 750)
P07.00	Extremely low birth weight newborn, unspecified weight	5 630 (16.1%)	152 (20.3%)
P07.01	Extremely low birth weight newborn, < 500 grams	1 668 (4.8%)	39 (5.2%)
P07.02	Extremely low birth weight newborn, 500–749 grams	9 397 (26.9%)	197 (26.3%)
P07.03	Extremely low birth weight newborn, 750–999 grams	10 715 (30.7%)	257 (34.3%)
P07.10	Other low birth weight newborn, unspecified weight	6 214 (17.8%)	157 (20.9%)
P07.14	Other low birth weight newborn, 1000–1249 grams	9 990 (28.6%)	211 (28.1%)
P07.15	Other low birth weight newborn, 1250–1499 grams	6 347 (18.2%)	114 (15.2%)
P07.16	Other low birth weight newborn, 1500–1749 grams	304 (0.87%)	29 (3.9%)
P07.17	Other low birth weight newborn, 1750–1999 grams	158 (0.45%)	10 (1.3%)
P07.18	Other low birth weight newborn, 2000–2499 grams	142 (0.41%)	10 (1.3%)
P07.20	Extreme immaturity, unspecified weeks	3,468 (9.9%)	96 (12.8%)
P07.21	Extreme immaturity, gestational age < 23 weeks	1 416 (4.1%)	31 (4.1%)
P07.22	Extreme immaturity, gestational age 23 weeks	2 304 (6.6%)	57 (7.6%)
P07.23	Extreme immaturity, gestational age 24 weeks	5 214 (14.9%)	107 (14.3%)
P07.24	Extreme immaturity, gestational age 25 weeks	6 095 (17.4%)	166 (22.1%)

[1]Note: Categories are not mutually exclusive, as infants may carry codes across multiple P07 subcategories (e.g., both a birth-weight code and a gestational-age code). Percentages reflect the proportion of each cohort with at least one code in that category. [2]ICD-10 = International Classification of Diseases, 10th Revision

ICD-10[2] Code	Description	Substance Non-Exposed (N = 34 961)	Substance-Exposed (N = 750)
P07.25	Extreme immaturity, gestational age 26 weeks	6 572 (18.8%)	162 (21.6%)
P07.26	Extreme immaturity, gestational age 27 weeks	6 905 (19.8%)	160 (21.3%)
P07.30	Preterm newborn, unspecified weeks	15 036 (43.0%)	394 (52.5%)
P07.31	Preterm newborn, gestational age 28 weeks	7 092 (20.3%)	160 (21.3%)
P07.32	Preterm newborn, gestational age 29 weeks	6 143 (17.6%)	172 (22.9%)
P07.33	Preterm newborn, gestational age 30 weeks	5 608 (16.0%)	99 (13.2%)
P07.34	Preterm newborn, gestational age 31 weeks	276 (0.79%)	13 (1.7%)
P07.35	Preterm newborn, gestational age 32 weeks	223 (0.64%)	10 (1.3%)
P07.36	Preterm newborn, gestational age 33 weeks	144 (0.41%)	10 (1.3%)
P07.37	Preterm newborn, gestational age 34 weeks	145 (0.41%)	10 (1.3%)
P07.38	Preterm newborn, gestational age 35 weeks	108 (0.31%)	10 (1.3%)
P07.39	Preterm newborn, gestational age 36 weeks	249 (0.71%)	10 (1.3%)

[1]Note: Categories are not mutually exclusive, as infants may carry codes across multiple P07 subcategories (e.g., both a birth-weight code and a gestational-age code). Percentages reflect the proportion of each cohort with at least one code in that category. [2]ICD-10 = International Classification of Diseases, 10th Revision

A diagnosis of ROP (H35.1, any stage) was recorded in 620 of 750 substance-exposed infants (82.7%) compared with 24,294 of 34,961 non-exposed infants (69.5%; OR 2.09, 95% CI 1.73–2.53; $p < 0.00001$) (Table 3).When stratified by ROP stage, the substance-exposed cohort demonstrated significantly higher rates of stage 1, 2, and 3 ROP compared with the non-exposed cohort (Table 3). Stage 4 ROP was also significantly more common in the substance-exposed group, though absolute case counts were small in both groups. Stage 5 ROP (retinal detachment) was not significantly different between groups; no stage 5 cases were identified in the substance-exposed cohort, compared with 53 cases (0.15%) in the non-exposed cohort ($p = 0.857$) (Table 3).

Table 3
Retinopathy of Prematurity Diagnosis and Stage1

ROP[2] Stage (ICD-10[3] Code)	Substance Non-Exposed (N = 34 961)	Substance-Exposed (N = 750)	OR[3] (95% CI[4])	*p*-value
Any ROP (H35.1)	24 294 (69.5%)	620 (82.7%)	2.09 (1.73–2.53)	< 0.00001
Unspecified stage (H35.10)	13 979 (40.0%)	383 (51.1%)	1.57 (1.36–1.81)	< 0.00001
Stage 1 (H35.12)	7 596 (21.7%)	270 (36.0%)	2.03 (1.74–2.36)	< 0.00001
Stage 2 (H35.13)	5 744 (16.4%)	189 (25.2%)	1.71 (1.45–2.03)	< 0.00001
Stage 3 (H35.14)	3 424 (9.8%)	107 (14.3%)	1.53 (1.25–1.89)	< 0.00001
Stage 4 (H35.15)	167 (0.5%)	10 (1.3%)	2.82 (1.48–5.35)	0.00048
Stage 5 (H35.16)	53 (0.2%)	0 (0.0%)	—	0.857

[1]Note: Stage categories may not be mutually exclusive as infants can have multiple stage codes recorded over time. [2]ROP=retinopathy of prematurity; [3]ICD-10 = International Classification of Diseases, 10th Revision; [3]OR=Odds Ratio; [4]CI=Confidence Interval

Across stages 1 through 3, the magnitude of association between substance exposure and ROP diagnosis was greatest for stage 1 disease (OR 2.03) and progressively attenuated for stage 2 (OR 1.71) and stage 3 (OR 1.53) disease, though all three comparisons remained highly statistically significant ($p < 0.00001$ for all) (Table 3).

To assess whether the observed differences in ROP outcomes could be explained by differences in underlying prematurity severity, the two cohorts were compared across ICD-10 P07 diagnosis categories. Overall, the two cohorts showed broadly comparable rates across most weight and gestational-age subcategories, with differences generally within 5 percentage points. The substance-exposed cohort showed slightly higher rates of extremely low birth weight (67% vs. 64%), extreme immaturity of newborn (71% vs. 68%), and other preterm birth (78% vs. 71%) diagnoses. The largest gaps were observed in the “unspecified weeks of gestation” (P07.30: 53% vs. 43%) and “unspecified weight”

(P07.10: 28% vs. 18%) subcategories, which most plausibly reflect differences in documentation completeness between cohorts rather than true differences in gestational age or birth weight, since more granular, week-specific and weight-band-specific subcodes did not show comparable gaps. Across individual gestational-age weeks (23–36 weeks) and weight bands, differences between groups were generally small (≤ 5 percentage points) and did not follow a consistent direction, supporting overall comparability of prematurity severity between the substance-exposed and non-exposed cohorts.

Discussion

As rates of prenatal substance exposure continue to rise, understanding its relationship to ROP has become an increasingly relevant clinical question. In this retrospective cohort of infants born ≤ 30 weeks' gestation and/or under 1500 g, prenatal substance exposure was associated with significantly higher rates of ROP overall and at stages 1 through 4 specifically, with approximately twice the odds of stage 1 disease and roughly 1.5- to 1.7-fold higher odds of stage 2 and stage 3 disease compared with non-exposed infants. Notably, this association was observed despite broadly comparable distributions of prematurity severity between groups across ICD-10 birth weight and gestational age categories, with most subcategory differences within 5 percentage points and no consistent direction favoring either cohort. This suggests that the elevated ROP risk in substance-exposed infants is not simply attributable to substance-exposed infants being more premature and instead raises the possibility of an independent contribution of prenatal substance exposure to ROP risk.

The relationship between prenatal substance exposure and ROP, specifically, has received relatively little study. The strongest population-level evidence on the influence of prenatal substance exposure on eye development comes from a Quebec birth cohort of nearly 800 000 infants, which found that those children with prenatal substance exposure had a higher incidence of childhood hospitalizations for eye disorders, 47.0 versus 32.0 per 10 000 person-years, corresponding to a 23% increased hazard of hospitalization for any eye disorder after adjustment for patient characteristics. [10] That study, however, examined a composite outcome of eye disorders broadly, including strabismus and retinal detachment, rather than ROP staging specifically, and was not restricted to the extremely preterm population in which ROP risk is concentrated. Case reports and small studies have described cocaine-exposed infants with ROP-like fundus changes, persistent hyperplastic primary vitreous, and optic nerve abnormalities. [11] This literature, along with the findings of this study, suggests a plausible but incompletely characterized association between prenatal substance exposure and retinal vascular outcomes in premature infant and requires further examination at scale, using ROP stage as a specific, standardized outcome in a population matched for degree of prematurity.

The findings of this study may support heightened vigilance for ROP in preterm infants with documented prenatal substance exposure and could inform discussions around screening frequency or threshold adjustments in this subgroup, pending validation in prospective, chart-confirmed cohorts. They also underscore the importance of coordinated care between neonatology, ophthalmology, and addiction medicine/social work services for substance-exposed neonatal intensive care patients. Substance-

exposed infants often have fragmented prenatal care and are more likely to experience gaps in postnatal follow-up. [12] Additionally, ROP predisposes patients to additional pediatric ophthalmic conditions such as strabismus, amblyopia, and myopia[13], findings which may be missed if this population is not specifically flagged for consistent ophthalmologic surveillance. Identifying prenatal substance exposure as a marker of elevated ROP risk could therefore help prioritize limited screening resources toward infants who might otherwise be lost to follow-up and could support the case for embedding ophthalmology referral pathways directly into the discharge and outpatient planning process for this population.

Several limitations should be considered when interpreting these findings. First, this was a retrospective, claims/electronic health record (EHR)-coding–based study; both exposure status and ROP diagnosis were ascertained via ICD-10 codes rather than direct chart or fundus examination review, introducing potential misclassification in both directions (documented limitations of TriNetX-based methodology have been described elsewhere). [14] The substance-exposed and non-exposed cohorts differed substantially in size (750 vs. 34,961), and without matching on additional covariates such as comorbid neonatal conditions (e.g., duration of supplemental oxygen, sepsis, intraventricular hemorrhage), residual confounding cannot be excluded even though prematurity severity, as measured by ICD-10 P07 birth weight and gestational age categories, was broadly comparable between groups. Lastly, this study could not assess dose, timing (trimester), or specific substance class of exposure, all of which may differentially affect retinal vascular development. Finally, findings are limited to healthcare organizations contributing to the TriNetX network and may not generalize to all clinical settings.

Prospective, chart-validated studies are needed to confirm these associations with directly verified ROP staging and more granular exposure data (substance class, timing, and dose). Future work should also explore whether the association between substance exposure and ROP is mediated by specific postnatal factors (e.g., growth trajectory, withdrawal-related instability) versus a more direct vasculopathic mechanism, and whether risk differs by specific substance class (opioid vs. stimulant vs. polysubstance exposure).

Conclusion

In this large retrospective cohort study of infants born ≤ 30 weeks' gestation and/or under 1500 grams at birth, prenatal substance exposure was associated with significantly higher odds of ROP overall and across stages 1 through 4, despite broadly comparable prematurity severity distributions between groups. These findings support consideration of prenatal substance exposure as an independent risk factor for ROP development and severity, warranting further prospective study and possible incorporation into risk-stratified screening discussions for this vulnerable population.

Declarations

Conflict of Interest:

The authors have no conflicts of interest to disclose.

Ethics Statement

This study was reviewed by the Penn State University Institutional Review Board and was determined to be exempt as human subjects research, STUDY00030144

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Author Contributions:

Ms. Shivani Bhargava conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Ms. Ananya Sridharan carried out the data analyses and critically reviewed and revised the manuscript.

Dr. Tammy Corr participated in the design of the study, provided oversight of the study execution, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Availability of Materials:

Data were derived from the TriNetX Research Network, a federated platform providing access to aggregated, deidentified electronic health record data. Due to TriNetX's data use agreement and federated access model, the underlying patient-level data are not publicly available; aggregate query results supporting the findings of this study are available from the corresponding author upon reasonable request.

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