

Effect of Maternal Drug Abuse on Retinopathy of Prematurity

Justin Harvey^{1*}, Obadah Moushmouth², Steven Fish¹, Jad Ramadan³ and Ghassan Ghorayeb¹

¹Department of Ophthalmology, West Virginia University, Morgantown, WV, USA

²School of Medicine, West Virginia University, Morgantown, WV, USA

³Rockefeller Neuroscience Institute, West Virginia University, Morgantown, WV, USA

*Corresponding Author: Justin Harvey, Department of Ophthalmology, West Virginia University, Morgantown, WV, USA.

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Abstract

Objective: To assess the effects of maternal drug abuse on the incidence, prevalence and severity of retinopathy of prematurity (ROP).

Introduction: ROP is a leading cause of neonatal blindness worldwide. Failure to reach mature retinal vascularization milestones in utero leads to rapid neovascularization, hemorrhage, retinal detachment, and vision loss. Substance use reported among pregnant women include smoking cigarettes, using alcohol, and the use of illicit substances. This has been linked to significant fetal morbidity and mortality. West Virginia stands at the forefront of this endemic, with opiate use during pregnancy having quadrupled between 1999 and 2014. The effect of maternal perinatal drug misuse on ROP has not yet been established.

Methods: This is a retrospective chart review assessing 422 premature newborns that met screening criteria between 2015 - 2018. The charts were assessed for ROP status, birth weight, maternal age, treatment type, gestational age, incidence of ROP by year, zone, stage, and evidence of "plus" disease. Of these, 282 newborn charts that included maternal drug data and urine drug screens were analyzed for maternal illicit substance abuse.

Results: The prevalence of treatable Type 1 ROP was stable between 2015-2018 with mean of $9.95 \pm 1.9\%$. 33% of mothers in our study population had a positive urine drug screen. The most prevalent was tetrahydrocannabinol in 18.4% followed by opiates in 17.0%. Gestational age ($p < 0.01$) and birth weight ($p < 0.01$) differ among "type 1 (T1)", "type 2 (T2)", and "no ROP" classes. Multiple gestation pregnancy ($p = 0.21$), maternal age ($p = 0.43$), gravida ($p = 0.43$), para ($p = 0.08$) and maternal illicit substance use ($p = 0.99$) were found to be independent of ROP class.

Conclusion: This study supports previous findings that gestational age and birth weight are significant factors in ROP pathogenesis. There was an exceptionally higher (33%) percentage of positive urine drug screens in our sample population and nearly 6x higher prevalence of gestational opiate use when compared to prior studies, however there was no association between maternal gestational drug abuse and the presence of ROP.

Keywords: Retinopathy of Prematurity; ROP; Opiates; Drug Abuse; Illicit Substance; Urine Drug Screen (UDS)

Abbreviations

ROP: Retinopathy of Prematurity; UDS: Urine Drug Screen; T1: Type 1; T2: Type 2; THC: Tetrahydrocannabinol; VEGF: Vascular Endothelial Growth Factor; IGF-1: Insulin-Like Growth Factor-1; GA: Gestational Age; EPO: Erythropoietin

Introduction

Perinatal maternal substance abuse has become increasingly concerning as maternal drug dependence increases. It has been reported that among pregnant women 15.9% smoke cigarettes, 8.5% use alcohol, and 5.9% use illicit substances while pregnant [1]. The use of illicit substances have been linked to fetal compromise and various comorbidities such as miscarriage, low birth weight, ectopic pregnancy, increased infant mortality rate, intrauterine growth restriction, abruptio placenta, and small for gestational age [1,2]. Gestational opiate use in particular has been well linked to poor maternal and perinatal outcomes such as respiratory depression, microcephaly, sudden infant death syndrome and neonatal abstinence syndrome [1-3].

The opiate crisis is highly prevalent across the United States. From 1999-2017 almost 400,000 people died from opiate use, accounting for a majority of drug related deaths in 2017 [4]. In 2012, West Virginia had an estimated 138 prescriptions per 100 persons [5], placing this state at the forefront of this endemic. Pregnant patients have not been spared, with over one-third of reproductive aged women filling a prescription for opiate medications each year from 2008-2012 [6]. According to the Healthcare Cost and Utilization project, opiate use during pregnancy has quadrupled from 1.5 to 6.5 per 1,000 deliveries between 1999-2014 alone [7]. The effect of maternal perinatal drug abuse on ROP has not yet been established.

ROP is a leading cause of neonatal blindness worldwide [8]. The developing retina in utero is initially supplied by the hyaloid system, which transitions to new blood vessel formation at approximately 12 weeks' gestational age (GA) and is complete by 21 weeks' GA. At approximately 17 weeks GA, angiogenesis is initiated following the signals produced by the vascular framework and is complete by 36 - 40 weeks [9,10]. Failure to reach these milestones in utero followed by abrupt changes in retinal oxygen and hormonal concentrations lead to rapid neovascularization, hemorrhage, retinal detachment, and vision loss.

Screening is conducted on all premature infants less than 1500g birth weight or less than 31 weeks GA [11]. Screening occurs at either 31 weeks GA or 4 weeks' chronological age. These screening exams are repeated every 1 - 3 weeks until criteria for screening cessation is met [11]. If the threshold for treatment is reached, treatment is initiated in the form of cryotherapy, laser photocoagulation, VEGF (vascular endothelial growth factor) inhibitors, or surgical intervention.

In this study, we investigated patients that met initial premature screening criteria at a large tertiary care hospital in West Virginia, United States. This paper serves to investigate if there may be a correlation between ROP and maternal drug abuse.

Materials and Methods

In this retrospective chart review study, we analyzed 422 premature newborns presenting to a single large tertiary medical center from 2015-2018 for ROP screening exams. Screening criteria from the Evidence-Based Screening Criteria for Retinopathy of Prematurity (2002) [11] was employed. Variables such as ROP status, birth weight, maternal age, ROP treatment type, gestational age, incidence of ROP by year, zone, stage, and evidence of plus disease was assessed [12]. A majority of these patients were seen inpatient while in the neonatal intensive care unit, but some were seen at follow-up clinic as outpatients. ROP status was assigned based on guidelines from The International Classification of Retinopathy of Prematurity Revisited (2005) [13]. The patients were assessed by board certified ophthalmologists at West Virginia University.

Of the 422 patients included in this study for initial analysis, 282 of these patients had records including a maternal urine drug screen (UDS) and were analyzed. The urine drug screens were performed upon admission to the obstetrics unit prior to receiving any maternal opioid analgesics. Umbilical cord blood and meconium screening was not included in this study due to inconsistency in performing these studies. Maternal age, gravida and para, multiple gestation status, and maternal urine drug screens were analyzed. Urine drug screens were either documented based on direct results within our electronic medical record or as documented in newborn history and physical. Subjective admission to drug use was accepted, but a subjective denial of drug use without supporting UDS was excluded from the study. Maternal charts were directly linked to the neonate through EPIC (Epic Systems Corporation, Madison, Wisconsin, US) electronic medical record and allowed direct access to this information. No maternal identification information was collected or recorded in accordance

with the IRB. All statistical tests were conducted using R Software version 3.6.1. The relationship between ROP and gestational age/birthweight was analyzed using the Kruskal Wallis test (due to skewness in both predictors). All remaining associations were analyzed using Fisher’s Exact Test. The critical p-value level was set at $p \leq 0.05$.

Results

Of the 422 charts analyzed, there were 121 ROP screenings performed in 2015, 84 in 2016, 117 in 2017, 100 in 2018 (Table 1). 361 (85.6%) had no ROP, 47 (11.1%) had T1 ROP, and 14 (3.3%) had T2 ROP at their most pathologically advanced stage. There were 11 (9.1%) found to have T1 ROP in 2015, 10 (11.9%) in 2016, 9 (7.7%) in 2017 and 17 (11.1%) in 2018 (Table 1). 89.4% of patients with T1 ROP had evidence of “plus” disease. ROP progression was seen in 14.5% of cases. Treatment included 17 receiving laser and 30 receiving anti-VEGF treatment. Of the anti-VEGF group, 27 received bevacizumab and 3 received ranibizumab.

Year	Screenings	Type 1 ROP	Percent Type 1
2015	121	11	9.1 %
2016	84	10	11.9 %
2017	117	9	7.7 %
2018	100	17	11.1%
Total	422	47	11.1 %

Table 1: Type 1 ROP by year.
ROP: Retinopathy of Prematurity.

282 of the initial 422 patients were included for drug use analysis based on maternal UDS data availability. Mean gestational age for mothers with no ROP was 29.67 ± 2.58 and 24.51 ± 1.60 for T1 (Table 2). Mean maternal age overall was 26 ± 5.97 years. Mean birth weight for no ROP was 1369.3 ± 449.4 grams and 712.5 ± 190.7 grams for T1 (Table 3). 71.3% were delivered by cesarean section and 28.0% delivered vaginally, with 0.7% unknown. Of the 282 newborns receiving screenings, 253 (89.7%) did not have ROP, 23 (8.2%) had type 1 ROP, and 6 (2.1%) had type 2 ROP. 95 (33.7%) of the patient’s mothers had positive or reported positive urine drug screens (Table 4).

Class	GA Min.	GA 1 st Qu.	GA Median	GA Mean	GA 3 rd Qu.	GA Max.	SD
No ROP	22	28	30	29.67	32	36	2.58
t1	22	24	24	24.51	25	31	1.6
t2	23	24.25	25	25.43	26	29	1.55

Table 2: Gestational age by ROP type.
GA: Gestational Age; Qu: Quartile; Max: Maximum; Min: Minimum; t1: Type 1; t2: Type 2; ROP: Retinopathy of Prematurity.

Class	BWt Min.	BWt 1 st Qu.	BWt Median	BWt Mean	BWt 3 rd Qu.	BWt Max.	SD
No ROP	155	1042.5	1400	1369.3	1655	2870	449.4
t1	470	585	650	712.5	777.5	1360	190.7
t2	520	605	785	805	840	1470	250.3

Table 3: Birthweight by ROP type.
GA: Gestational Age; Qu: Quartile; Max: Maximum; Min: Minimum; t1: Type 1; t2: Type 2; ROP: Retinopathy of Prematurity

Drug	Number Positive UDS (N = 282)	Percent %	Association with ROP (p-value)
Any substance	95	33.7%	0.99
THC	52	18.4%	0.47
Opiates	48	17.0%	0.84
Benzodiazepines	10	3.5%	NA
Amphetamine	10	3.5%	0.38
Cocaine	7	2.5%	NA
Other	6	2.1%	NA

Table 4: ROP and maternal urine drug screen positivity.

UDS: Urine Drug Screen; ROP: Retinopathy of Prematurity; THC: Tetrahydrocannabinol.

Gestational age ($p < 0.01$) and birth weight ($p < 0.01$) differ among T1, T2, and “no ROP” classes (Figure 1 and 2). Multiple gestation pregnancy ($p = 0.21$), maternal age ($p = 0.43$), gravida ($p = 0.43$), para ($p = 0.08$) and UDS ($p = 0.99$, Table 4) were found to be independent of ROP class. P-values for specific substances in UDS are provided in Table 4, none of which reached statistical significance.

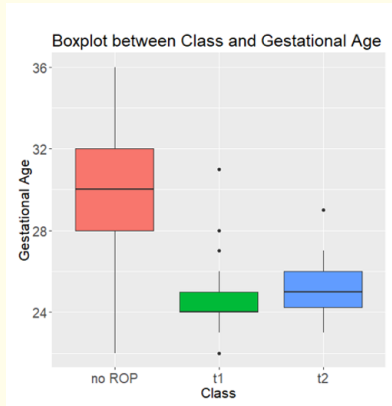


Figure 1: Boxplot between class and gestational age. T1 (type 1 ROP); T2 (type 2 ROP). p -value < 0.00001 . Kruskal Wallis test.

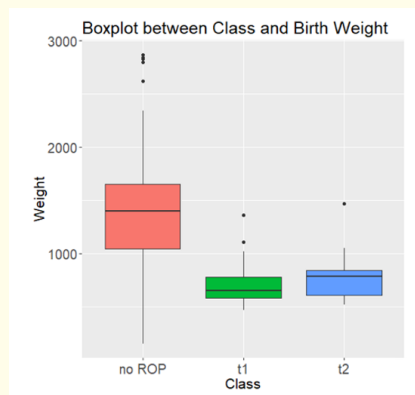


Figure 2: Boxplot between class and birth weight. T1 (type 1 ROP); T2 (type 2 ROP). p -value < 0.00001 . Kruskal Wallis test.

Discussion

ROP is strongly associated with premature birth, most notably gestational age less than 31 weeks [11,14]. This disease has also been established to be strongly associated with low birthweight (less than 1500 grams) and postpartum neonatal supplemental oxygen use [14]. Our data supports prior literature [14,15] showing a strong and significant association between gestational age and birth weight with ROP (Figure 1 and 2), supporting our understanding of the disease risk factors. Also, these results suggest that our sample population is consistent with prior studies, thus making the results more applicable to other patient populations. A thorough review by Kim, *et al.* (2018) has noted that there have been many other proposed associations with ROP and have found conflicting study results [14].

The pathogenesis of ROP includes hyperoxic and relative hypoxic stages. In the neonatal postpartum period, the premature respiratory system quickly leads to pulmonary insufficiency and hypoxia, requiring supplemental oxygen utilization. This iatrogenic hyperoxic environment causes vasoconstriction and downregulation VEGF and erythropoietin (EPO) leading to temporary cessation of vascular proliferation. Similarly, withdrawal of maternal factors such as insulin-like growth factor-1 (IGF-1) and poly-unsaturated fatty acids contributes to downregulation of this process. This results in an overall hypoxic retina. Prior to 32 weeks, photoreceptors in the inner and outer retina are not fully mature and have minimal oxygen requirements. As these cells mature and develop increased oxygen metabolism, a relative hypoxic state is induced. This leads to upregulation of VEGF and EPO to alleviate this metabolic oxygen deficit. The response is continuation of core vasculature as well as rapid new vessel formation. The immature vasculature is at increased susceptibility to fluid and protein extravasation into the surrounding retina and vitreous. This neovascularization may also proliferate anteriorly into the vitreous leading to retinal traction and potential detachment [10,16].

In this study, we investigated several drugs of abuse, but wanted to pay close attention to the use of opiates given the current opiate crisis in the United States [4]. Our data analysis revealed a stable prevalence of ROP exams as well as T1 ROP percentage between 2015 - 2018 (Table 1). While short-term opiate use has been reported safe during breastfeeding [17], gestational opiate use has been associated with deleterious health effects on both the mother and fetus [1-3]. Similarly, the study by Whiteman, *et al.* in 2014 that analyzed healthcare costs between 1998 - 2009 concluded that there are increased healthcare costs estimated at \$1500 with maternal perinatal opiate use [18]. In line with this, Ahmad, *et al.* (2019) estimated an increased length of stay of 0.8 days and increased cost of \$3,797 [1]. Unfortunately, the effects of maternal opiate use do not stop after delivery. Opiate use contributes to neonatal abstinence syndrome and often requires intensive care treatment. Patrick, *et al.* (2015) reported a 5x increase in neonatal abstinence syndrome from 2000 - 2009 [19] which ultimately drives up healthcare costs and increases neonatal morbidity and mortality. While gestational opiate use has been associated with several potential birth defects such as congenital heart defects, neural tube defects, and gastroschisis [3], it has not been investigated as an independent risk factor for ROP.

Of the initial 422 infant and maternal charts reviewed from 2015 - 2018, only 282 mothers had either documented urine drug screens or subjectively supplied information on illicit drug use. We elected to exclude patients with subjectively negative UDS statuses as this was thought to compromise the validity of the study. Some were found to be positive through UDS obtained immediately prior to delivery while others were considered positive based subjective admission to illicit substance use.

A study by Whiteman, *et al.* in 2014 found that approximately 5% of gestational women were UDS positive [18], however our study population revealed 33% of mothers with a positive UDS. The most common substance was tetrahydrocannabinol (THC) at 18.4% followed by opiates at 17% (Table 4). Many of these UDSs were polysubstance positive. A study by Ahmad, *et al.* (2019) found that mothers with adult drug dependence were at 487 times higher risk for opioid abuse, followed by increased risks of cannabis and stimulant abuse [1]. In our study there were no newborns with ROP delivered by mothers with UDS positivity for benzodiazepines, cocaine, or other miscellaneous substances. This should be investigated further as our sample size of mothers using these substances was small (N = 23, Table 4).

Despite UDS prevalence of opiate and THC abuse of 17.0% and 18.4% respectively, there was no association with development of ROP. It was theorized that there may be significance to amphetamine abuse due in part of its vasoconstricting effects and potentially inducing a relative hypoxic state in utero and warrants further investigation, however no significant association between amphetamines and ROP

was found ($p = 0.38$, table 4). Likewise, it would be useful to compare this to the ROP status associated with maternal cocaine use, however our study contained no cocaine-positive urine drug screens or subjective admission to gestational cocaine use.

Limitation of the Study

One major limitation of this study includes limited access to records on patients transferred from outside facilities. Nearly half of our initial study population had to be excluded from analysis due to lack of a maternal UDS on file. Unfortunately, many of these transferred patients were transferred for ophthalmologist treatment of ROP at our medical center and would have been very valuable to the study. Relying on patient-reported drug use when a UDS was unavailable was thought to compromise the study's validity and any results drawn off of this would be unreliable. Another limitation of this study would be controlling for prematurity as a confounding factor. It can be appreciated that a majority of the deliveries were performed via cesarean section (71.3%), reflecting the nature of premature deliveries. Had our results approached significance, the newborns would need to be stratified based on gestational age and birth weight to eliminate the confounder as accepting maternal drug abuse as the cause of ROP, where ultimately it may have been premature delivery. This could be accomplished but would require a significantly larger sample size. Lastly, using a single UDS only provides us with a one cross-section of data during the length of pregnancy. The various washout times of the substances tested could have been missed and it is possible that the number of positive UDSs may have been significantly higher.

Future studies on this topic could investigate the effects of maternal smoking and alcohol use on ROP. At the moment, however, there is no routinely performed objective test at our institution to measure gestational alcohol and nicotine use. Also, as previously mentioned, investigating the effects of vasoconstricting illicit substances, such as amphetamines and cocaine on ROP, could be insightful.

Conclusion

Gestational illicit substance abuse is at an all-time high. Our cohort had maternal drug screen positivity at over 33%, nearly 7x higher than previously described. However, at this time we have no evidence to support that gestational illicit substance use influences the development of ROP.

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Conflicts of Interest

None of the authors listed have identified any conflicts of interest with this study.

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