Risk factors for clinically significant intra-ventricular hemorrhage in pregnancies complicated by preterm premature rupture of membranes

Giamberardino W[1], Winn VD[2], Armstrong J[1,3*]

[1]Department of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, USA
[2]Department of Obstetrics and Gynecology, Stanford University School of Medicine, USA
[3]Department of Pediatrics, University of Colorado Anschutz Medical Campus, USA

Abstract

Objectives: Preterm birth is a major cause of adverse perinatal outcomes, including intraventricular hemorrhage (IVH). IVH has been shown to contribute to lasting neurological disability, however the role of maternal characteristics and potentially modifiable risk factors that contribute to these outcomes have not been well defined. We sought to determine predictors of IVH in pregnancies complicated by early preterm premature rupture of membranes (PPROM).

Study design: We performed a retrospective cohort study of all singleton pregnancies with early PPROM <32 weeks GA and delivery >22 weeks GA at University of Colorado Hospital (UCH) from 1/1/2007-12/31/2011. Clinically significant IVH (Grade III or IV) was the primary outcome of this study. To determine independent predictors of IVH we created a multivariate model including all univariate covariates with p-value of ≤ 0.10.

Results: In our cohort (n=229), when adjusted for non-white race, younger maternal age and increased BMI were independent predictors of clinically significant IVH (OR=1.4 CI 1.04-1.79, p=0.03; OR 1.2 CI 1.04-1.33, p=0.01, respectively). Female gender was also found to be an independent predictor of poor 5 minute APGAR (OR=2.3 CI 1.06-5.28, p=0.04).

Conclusions: In our cohort, infants born to younger mothers or mothers with higher BMI appear to be at increased risk for clinically significant IVH. Interestingly, on further analysis, we found that female newborns had a 2-fold greater risk of poor 5 minute APGAR of less than 7. Given these data, larger studies are warranted to examine modifiable and non-modifiable risk pregnancy that may be associated with IVH and subsequent adverse neurological outcomes in pregnancies complicated by early PPROM

Keywords: Intra-ventricular, Hemorrhage, Preterm birth, Pregnancy

Accepted on 29th October, 2021

Introduction

Preterm birth continues to be a significant problem with clear impact on morbidity and mortality of the newborn. Preterm birth affects 12% of live births in the United States and is a leading cause of infant mortality [1,2]. Currently, over one third of all infant deaths are attributed to preterm related causes [3]. Further, preterm birth is a major cause of adverse perinatal outcomes, including intraventricular hemorrhage (IVH). It has been shown that severe IVH (grade III or IV) alone portends poor neurological outcome in the premature infant regardless of other factors of prematurity [4].

Although there are numerous studies addressing the outcomes of premature birth and the role of neonatal factors, such as respiratory distress syndrome, gestational age, and early sepsis in the development of IVH, [5,6] it remains unclear if maternal or pregnancy factors may also contribute to the development of this adverse neurological outcome. Moreover, there is little data examining potentially modifiable variables of the pre-conception and pregnancy periods that may reduce the risk of developing clinically significant IVH in the premature newborn.

Despite accounting for 30%-40% of preterm deliveries, preterm premature rupture of membranes (PPROM) is understudied and presents a unique challenge considering that all PPROM pregnancies are at risk of preterm birth and thus the risks associated with early delivery, including IVH [7,8]. Consequently, investigating the possible predictors of IVH in pregnancies complicated by PPROM is a pertinent and important question considering that PPROM occurs in 1%-2% of all pregnancies in the United

States. Additionally, these mothers have upwards of a 30% increased risk of having preterm delivery and up to a 21% risk of PPROM in subsequent pregnancies [7,9].

We sought to determine maternal, pregnancy related, and fetal risk factors that contribute to the development of clinically significant IVH in the PPROM population. This information would allow for potential improvement in the counseling and management of these obstetric patients and their newborns given that IVH is known to contribute to lasting neurological disability and that these risk factors for IVH may be modifiable, andthus, mitigated.

Methods

We performed a retrospective cohort study of all singleton pregnancies with PPROM born at the University of Colorado Hospital (UCH) from January 1, 2007 through December 31, 2011. The protocol for this study was approved by the Colorado Multiple Institutional Review Board (COMIRB), and the University of Colorado Hospital.

Our cohort included cases identified through the UCH Perinatal Database. This database collects maternal, pregnancy, delivery, and neonate data on all pregnancies delivering at the UCH. Data is collected by direct patient interview, performed by trained research nurses, and medical chart abstraction. Cases were confirmed by independent chart review of all patients (W.G.), with confirmation by a neonatal neurologist (J.A.).

Inclusion criteria for PPROM in this study were rupture of membranes <32 weeks gestational age without active labor and cases were verified by abstraction of the medical chart for diagnosis of PPROM as recorded by the treating physician.

Variables captured by the Perinatal Database included for analysis were maternal factors: racial background, ethnicity, age, smoking, hypertension (HTN) diabetes, pre-pregnancy body mass index (BMI), primigravida status; pregnancy factors: chorioamnionitis, and fetal factors: neonatal weight, sex, hypoglycemia, respiratory distress, 1 minute and 5 minute APGAR scores of less than 5 and 7, and disposition (NICU, well baby, demise). Also included were data on GA at time of PPROM, GA at delivery, and latency period from PPROM to delivery (days). These variables were chosen as they look at both the modifiable and non-modifiable risk factors in the pre-conception, pregnancy, and post-partum periods that may contribute to IVH in the newborn. The primary outcome of this study was established a priori and defined as intraventricular hemorrhage in the newborn of grade III or IV as identified by cranial ultrasound.

Data analysis included cases of PPROM as previously defined. We compared dichotomous variables by using χ^2 analysis (or Fisher's exact test when an expected cell size was <5) and continuous variables by using the t test. To assess predictors of IVH we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression. GA at time of PPROM, maternal age, and maternal BMI were treated as both continuous and trichotomous variables. GA at time of PPROM was trichotomized as <24, 24 to 28, and >28 to 32 wks. Maternal age was defined as <18, 18 to 30, and >30 years, and pre-pregnancy BMI was classified as <20, 20 to 30, and >30. Additionally, GA at delivery was treated as a continuous and quartiled variable defined by 22 to 24, >24 to 28, >28 to 32, and >32 wks.

To determine independent predictors of grade III or IV IVH we created a multivariate model, including all univariate covariates with a P value of ≤ .10. We used Stata 12.1 (Stata Corp, College Station, TX) to perform all statistical calculations, with $p<0.05$ considered significant.

Results

We identified 229 eligible cases of PPROM, representing approximately 10% of all deliveries (Table 1). The cohort demographics were representative of the Rocky Mountain Region with 188 (82%) of maternal fetal dyads being white and 94 (41%) of Hispanic ethnicity. Mean maternal age was 27 years. Mean gestational age at time of PPROM and at time of delivery were 27 and 29 weeks respectively, with a mean latency from time of PPROM to delivery of 13.9 days. Almost 50% of the pregnancies were complicated by clinical chorioamnionitis (n=107). The majority of newborns were male (n=141; 60%). Less than 5% (n=9) of newborns transitioned to the well-baby unit post-partum. Of all 229 deliveries, 31 (14%) resulted in neonatal demise, either at the time of delivery or prior to disposition from the NICU or the well-baby unit. In the 31 deliveries that ultimately resulted in neonatal demise the median GA at delivery was 241/7, with a range from 220/7 to 314/7 weeks.

Table 1. *Cohort Demographic*

Maternal Characteristics	**(%)**
Age, mean (SD)	27 (6.43)
Race	
White	188/229 (82)
Non-white	41/229 (18)
Ethnicity	
Hispanic	94/228 (41)
Non-Hispanic	134/228 (59)
Primigravida	64/229 (28)
Modifiable Risk Factors	
BMI, mean (SD)	26 (6.83)
Diabetes	25/228 (11)
HTN	7/229 (3)
Smoking	43/228 (19)

Pregnancy Characteristics	
Chorioamnionitis	107/229 (47)
Gestational age at PPROM, mean (SD)	27 (3.63)
Gestational age at delivery, mean (SD)	29 (3.39)
Latency time to delivery (days)	13.9 (19.72)
Newborn Characteristics	
Female gender	88/228 (39)
Birth weight (g), mean (SD)	1326 (556.9)
APGARs	
APGAR 1 minute <5	105/228 (46)
APGAR 1 minute <7	155/228 (68)
APGAR 5 minutes <5	37/228 (16)
APGAR 5 minutes <7	84/228 (37)
Complications	
Hypoglycemia	10/229 (4)
IVH grade 3	6/229 (3)
IVH grade 4	1/229 (0.44)
Respiratory distress syndrome	156/229 (68)
Disposition	
Well-baby	9/229 (4)
NICU	189/229 (83)
Demise	31/229 (14)
Median GA of Demise	241/7

Earlier gestational age at PPROM or delivery, younger maternal age, and increased maternal BMI were univariate predictors of clinically significant IVH. When adjusted for non-white race, younger maternal age (OR=1.4, CI 1.04-1.79, p=0.03) and increased BMI (OR=1.2, CI 1.04-1.33, p=0.01) were the only independent predictors of clinically significant IVH (Table 2).

Table 2. *Independent Predictors of Intraventricular Hemorrhage Grade III/IV*

	OR	(95%CI)	p
Gestational Age at PPROM	0.8	(0.64 - 1.05)	NS
Gestational Age at Delivery	0.8	(0.38 - 1.58)	NS
Birth Weight	1.0	(0.99 - 1.01)	NS
Younger Maternal Age	1.4	(1.04 - 1.79)	0.03
Increasing Maternal BMI	1.2	(1.04 - 1.33)	0.01

NOTE: Adjusted for non-white race. NS indicates not significant.

Earlier gestational age at PPROM or delivery, clinical chorioamnionitis, increased maternal BMI, and newborn female gender were predictors of poor APGAR score of <7 at 5 minutes on univariate analysis. However, on multivariate analysis, female gender was the sole independent predictor of APGAR <7 at 5 minutes (OR=2.3, CI 1.06-5.28, p=0.04;) (Table 3). There were no independent predicators of 1 minute APGAR <7.

Table 3. *Independent Predictors of Poor 5 Minute APGAR <7*

	OR	(95%CI)	p
Gestational Age at PPROM	0.9	(0.75 - 0.98)	NS
Gestational Age at Delivery	0.8	(0.62 - 1.11)	NS
Birth Weight	1	(0.99 - 1.00)	NS
Female Gender	2.3	(1.06 - 5.28)	0.04
Chorioamnionitis	1.8	(0.85 - 3.89)	NS
Increasing Maternal BMI	1.1	(1.00 - 1.13)	NS

NOTE : NS indicates no significant.

Discussion

In this 5 year retrospective cohort study of maternal newborn dyads from pregnancies complicated by PPROM, we examined potential risk factors associated with clinically significant IVH. We chose the outcome of severe (grade III or IV) IVH as it is related to adverse neurological outcome in the infant and can result in lasting disability. We found that infants born to younger mothers or mothers with increased BMI are at increased odds for clinically significant IVH, regardless of newborn gender or gestational age.

Although earlier gestational age at PPROM or delivery was significant risk factors for clinically significant IVH on univariate analysis, gestational age was not an independent risk factor when adjusted for maternal age and BMI. This is contrary to Lu et al. [10]; we suspect that our underlying case mix was different as they did not delineate clinically significant IVH but rather any grade IVH in their analysis. Similar to prior studies, latency interval was not a risk factor for IVH [11,12].

Unlike a recent study, we demonstrated that preterm infants born to mothers with higher BMI appear to be at increased odds for clinically significant IVH [13]. Our findings may represent different racial and ethnic difference that may skew the data, as our mothers were predominantly Caucasian. Maternal obesity has been associated with increased serum pro-inflammatory cytokines, endothelial dysfunction, and placental inflammation [14-16]. Normal pregnancy is a hypercoagulable state and obesity enhances this process [17]. One may speculate that maternal obesity induces a secondary hypercoagulable state in the fetus, similar to the fetal inflammatory response. Rather than primary hemorrhage of the choroid plexus, IVH may result from a primary venous thrombus, analogous to periventricular hemorrhagic venous infarct seen in the term newborn. Given these results, maternal BMI represents a potentially modifiable variable when assessing the risk of clinically significant IVH in the preterm infant.

Similar to another study, 5 minute Apgar score was not associated with clinically significant IVH in our PPROM cohort [8]. Interestingly, on further analysis we found that female newborns had 2 fold greater odds of poor 5 minute APGAR of <7 compared to male newborns. It is difficult based on the size and follow up period of this study to interpret whether our finding relates to long term morbidity in this population. Yet, this finding is thought provoking since male infants are customarily expected to have worse outcomes (including low APGAR scores and adverse neurological outcomes) [9,18-20]. Our finding may be explained by gender differences in the fetal inflammatory response; animal models of preterm hypoxic brain injury demonstrate enhanced plasma fetal inflammatory markers among female newborns [21,22]. Additionally, our group has demonstrated increased cord blood IL-6 and IL-8 levels in female newborns compared to males within a PPROM cohort [23]. These findings may be due to the complex pro-inflammatory and anti-inflammatory relationship of these cytokines. This curious finding necessitates larger longitudinal studies of PPROM to help define gender effects on long term outcomes, including neurological disability.

Conclusion

While representing 5 years of data, our study is limited by a relatively small sample size. Despite the sample size, this cohort represents the largest to date showing a correlation between maternal BMI and maternal age on clinically significant IVH in pregnancies complicated by early PPROM and preterm birth. Larger, prospective studies are warranted to examine the role of maternal age and BMI on neurologic morbidity in pregnancies complicated by PPROM. Considering the increasing obesity epidemic and the prevalence of teenage pregnancy it becomes important to discern between modifiable and non-modifiable risk factors that may contribute to clinically significant IVH in PPROM pregnancies and even broader populations at risk for preterm birth to better counsel and manage these already complex patients.

Conflict of Interest

The authors disclose no conflicts of interest

Funding

NIH BIRCWH K12 KD HDO57022 and Maternal and Child Bureau 340B program H30MC24049

References

1. Shen TT, DeFranco EA, Stamilio DM, et al. A population- based study of race-specific risk for preterm premature rupture of membranes. Am J Obstet Gynecol. 2008; 199: 373e1-373e7.
2. Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2012. Natl Vital Stat Rep. 2013; 62: 1-20.
3. Mathews TJ, Mac Dorman MF. Infant mortality statistics from the 2010 period linked birth/infant death data set. Natl Vital Stat Rep. 2013; 62: 1-26.
4. Calisici E, Eras Z, Oncel MY, et al. Neurodevelopmental outcomes of premature infants with severe intraventricular hemorrhage. J Matern Fetal Neonatal Med. 2015; 28: 2115-2120.
5. Levene MI, Fawer CL, Lamont RF. Risk factors in the development of intraventricular haemorrhage in the preterm neonate. Arch Dis Child. 1982; 57: 410-417.
6. Linder N, Haskin O, Levit O, et al. Risk factors for intraventricular hemorrhage in very low birth weight premature infants: A retrospective case-control study. Pediatrics. 2003; 111: 590-595.
7. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med. 2006; 19: 773-782.
8. Gezer A, Parafit-Yalciner E, Guralp O, et al. Neonatal morbidity mortality outcomes in pre-term premature rupture of membranes. J Obstet Gynaecol. 2013; 33: 38-42.
9. Ment LR, Vohr BR, Makuch RW, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. J Pediatr. 2004; 145: 832-834.
10. Lu H, Wang Q, Lu J, et al. Risk Factors for intraventricular hemorrhage in preterm infants born at 34 weeks of gestation or less following preterm premature rupture of membranes. J Stroke Cerebrovasc Dis. 2016; 25: 807-812.
11. Manuck TA, Maclean CC, Silver RM, et al. Preterm premature rupture of membranes: Does the duration of latency influence perinatal outcomes? Am J Obstet Gynecol. 2009; 201: 414e1-414e6.
12. Park SH, Kim HJ, Yang JH, et al. Neonatal brain damage following prolonged latency after preterm premature rupture of membranes. J Korean Med Sci. 2006; 21: 485-489.
13. Faucett AM, Metz TD, DeWitt PE, et al. Effect of obesity on neonatal outcomes in pregnancies with preterm premature rupture of membranes. Am J Obstet Gynecol. 2016; 214: 287e1-287e5.
14. Challier JC, Basu S, Bintein T, et al. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. Placenta. 2008; 29: 274-281.
15. Roberts KA, Riley SC, Reynolds RM, et al. Placental structure and inflammation in pregnancies associated with obesity. Placenta. 2011; 32: 247-254.

16. Saben J, Lindsey F, Zhong Y, et al. Maternal obesity is associated with a lipotoxic placental environment. Placenta. 2014; 35: 171-177.

17. Sharma SK, Philip J, Whitten CW. Thromboelastography in preeclamptic patients. Reg Anesth. 1996; 21: 493-495.

18. Bekedam DJ, Engelsbel S, Mol BW, et al. Male predominance in fetal distress during labor. Am J Obstet Gynecol. 2002; 187: 1605-1607.

19. Sheiner E. The relationship between fetal gender and pregnancy outcome. Arch Gynecol Obstet. 2007; 275: 317-319.

20. Sheiner E, Levy A, Katz M, et al. Gender does matter in perinatal medicine. Fetal Diagn Ther. 2004; 19: 366-369.

21. Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. Dev Med Child Neurol. 2007; 49: 74-78.

22. Prout AP, Frasch MG, Veldhuizen R, et al. The impact of intermittent umbilical cord occlusions on the inflammatory response in pre-term fetal sheep. PLoS One. 2012; 7: e39043.

23. Armstrong-Wells J, Donnelly M, Post MD, et al. Inflammatory predictors of neurologic disability after preterm premature rupture of membranes. Am J Obstet Gynecol. 2015; 212: 212e1-212e9.

*Correspondence to

Jennifer Armstrong,

Department of Obstetrics and Gynecology

University of Colorado Anschutz Medical Campus

USA

E-mail: jennifer.armstrong@cuanschutz.edu