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Research Article

Examining the Association of Preeclampsia with Neonatal Neurodevelopmental Delay

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Abstract

Preeclampsia, a de novo development of hypertension in consort with proteinuria after 20 weeks of gestation is the prominent cause of morbidity and mortality in mother and neonates. This study sought to determine neonatal outcomes, including neurodevelopmental delays, associated with preeclampsia. A retrospective cohort study of all live births in 2014, stratified on presence of maternal preeclampsia at the time of delivery was conducted. Demographic, clinical, and laboratory data were reviewed. The primary outcome was the presence of neurodevelopmental delay, defined by ICD-9 and ICD-10 codes at 2-4 years. Of the 2878 live births, 450 (16%) were born to mothers with preeclampsia. Infants of pre-eclamptic mothers had lower birthweights (median: 2902g vs. 3271g, range 411-5659, p<0.0001), lower gestational age (median: 37 weeks vs. 39 weeks, range 23-42, p<0.0001), higher rates of multiple gestation, cesarean sections, hypoglycemia, thrombocytopenia, and prolonged length of stay. At follow-up, infants born to pre-eclamptic mothers had an increased risk of being diagnosed with neurodevelopmental delay (9.9% vs. 6.0%, p=0.0023) and speech delay (18.6% vs. 13.6%, p=0.0056) when compared to those infants born to mothers without preeclampsia. Maternal preeclampsia increases risk of neurodevelopmental delay in early childhood in addition to previously known risks to neonates.

Keywords: Neurodevelopmental delays; Pregnancy, Pre-eclampsia

Introduction

Preeclampsia is a de novo development of hypertension with proteinuria (defined as more than 3 grams of protein in urine per day) beyond 20 weeks' gestation [1]; it has an incidence of up to 10% and is a leading cause of maternal and fetal morbidity and mortality [1-4]. It is known to be associated with increased long-term risk of maternal health and detrimental fetal outcomes [1]. It is usually categorized according to its severity, i.e. mild, moderate, and severe. Severe preeclampsia is defined as severe hypertension with systolic pressure ≥160 mm Hg or diastolic pressure ≥110 mm Hg with confirmation on consecutive results within 15 to 30 minutes with one of the following: 1) new onset of cerebral or visual disturbances; 2) severe persistent right upper quadrant pain or epigastric pain unresponsive to medical management; 3) pulmonary edema; 4) proteinuria greater than 5 grams per day; 5) platelet count <100,000 platelets/Micro L; or 6) fetal growth restriction.

Preeclampsia has multi-dimensional risk factors and common causes are inflammatory processes, prior maternal diseases, familial predisposition, and geographical and racial variability [4]. The inflammatory process can occur during different stages of pregnancy and to varying degrees, and is more severe when it occurs earlier than 34 weeks of gestational age [4]. Inflammation is necessary for successful embryo implantation because an increase in immune cells (natural killer cells and macrophages) creates the ideal environment for blastocyst implantation. The placenta creates the optimal environment that promotes trophoblast cells to induce differentiation to replace endothelium and the vascular smooth muscle of spiral arteries. Lack of appropriate trophoblast differentiation and invasion may cause inadequate perfusion of the placenta, which will clinically present as preeclampsia [5].

There are multiple factors associated with preeclampsia that are responsible for giving rise to the spectrum of short and long-term adverse effects on mother and infant. Short-term adverse effects of preeclampsia include intrauterine growth restriction, thrombocytopenia, neutropenia, and early and late-onset sepsis [4]. Some of the long-term adverse effects that are studied and remain controversial are neurological impairments, including developmental delays (such as gross motor, fine motor or speech delays), autism spectrum disorders, and increased risk of hospitalization for metabolic, nutritional, endocrine, and hematologic diseases. Preeclampsia continues to have a high impact on the health system as it has numerous adverse effects on both mother and infant.

There is limited literature on neurodevelopmental delays in neonates born to pre-eclamptic mothers; hence forth association is not well established yet. This study evaluated the short-term and 2-4 year neurodevelopmental outcomes of neonates born to pre-eclamptic mothers.

Materials and Methods

This retrospective cohort analysis used prospectively collected data of all live births at Baylor Scott & White Health, Temple, Texas from January 1, 2014 to December 31, 2014. Infants with major congenital anomalies were excluded. Demographic, clinical, laboratory, and outcome data were collected by study personnel and were

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reviewed by senior authors to ensure the accuracy of the data. Infants were stratified based on the presence or absence of maternal preeclampsia, regardless of severity, at the time of delivery. Follow-up data on neurodevelopmental outcomes was collected at 2-4 years of age from January 1, 2016 to December 31, 2018. The Baylor Scott & White Health Institutional Review Board approved this study.

Preeclampsia was defined as: "presence of hypertension after 20th week of gestation in pregnancy without proteinuria" as defined by the American College of Obstetrics and Gynecology [1]. Neurodevelopmental status was defined using ICD-9 and 10 diagnostic codes for speech delay (315.39; F80.9), gross and/or fine motor delay (315.4; F82.0), and cognitive/global developmental delays (315.2; 315.9; F81.9; F88.0; F89.0; R62.50) diagnosed during in-patient or outpatient encounters All children remained in the same medical system for their follow-ups until two years of age.

Descriptive statistics included mean values and standard deviation for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and frequencies and percentages for categorical variables. For bivariate analysis, comparisons for non-ordinal categorical measures were conducted using $\chi 2$ or Fisher exact test, which comparisons for ordinal categorical variables and nonsymmetrical continuous variables were conducted using the Kruskal-Wallis test. Risk for developmental delay was predicted using a binary and stepwise logistic regression model, respectively, using the backwards selection procedure and model diagnostics, including the Hosmer-Lemeshow test and residual plots. Risk was reported as an odds ratio with a 95% confidence interval. SAS (version 9.4; SAS Institute, Cary, North Carolina) was used for all statistical analyses. Significance is indicated as $p < 0.05$.

Results

In 2014, there were 2878 live births at Baylor Scott and White Memorial Hospital. Of those, 450 (16%) were born to pre-eclamptic mothers while 2428 (84%) were born to mothers without preeclampsia. Clinical and demographic characteristics of the study population are depicted in table 1. Infants of mothers with preeclampsia were noted to have significantly lower birth weights (median: 2902g vs. 3271g, range 411-5659, p<0.0001), were more likely to be delivered via cesarean sections (44% vs. 28%, p<0.0001), had lower gestational ages (median: 37 weeks vs. 39 weeks, range 23-42, p<0.0001), and had higher rates of multiple gestation (mostly twin births) (p=0.0039). 26% (n=775) of the infants were admitted to the neonatal intensive care unit. Infants born to mothers with preeclampsia had higher rates of hypoglycemia (p=0.0029) and thrombocytopenia with platelet count reported below 100 thousand platelets/MicroL (p=0.0005) as well as increased length of hospital stay (median: 11 days vs. 5 days, interquartile range 3-17, p<0.0001) (Tables 2 & 3). Mothers with preeclampsia were 3.4 times (95% CI; 1.9, 6.1) more likely to have an infant with intrauterine growth restriction than those mothers without preeclampsia. At follow-up, infants born to pre-eclamptic mothers had an increased risk of being diagnosed with neurodevelopmental delay (9.9% vs. 6.0%, p=0.0023) and speech delay (18.6% vs. 13.6%, p=0.0056) when compared to those infants born to mothers without preeclampsia (Table 4).

	All infants	Non-PreE	PreE	*P*
Number of infants	**2878**	**2428**	**450**	
Vaginal delivery	69.30%	71.80%	55.60%	**<0.0001**
Caucasian	57.80%	57.40%	60.20%	**0.014**
Female gender	48.90%	48.70%	49.60%	**0.76**
Age of mother, years	26 (14-47)	26 (14-47)	27 (15-44)	**0.08**
Multiple gestation				**0.003**
Singleton	95.30%	95.80%	92.70%	
Twins or greater	4.70%	4.20%	7.30%	
Gestational age, weeks	39 (37.1-39.4)	39 (38.0-39.6)	37.4 (35.1-39.0)	**<0.0001**
Birth weight, grams	3217 (2818-3572)	3271 (2889-3600)	2903 (2320-3274)	**<0.0001**

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

Data shown as median (IQR) unless otherwise indicated; Bivariate analysis, comparisons for non-ordinal categorical measures were conducted using χ^2 or Fisher exact test, which comparisons for ordinal categorical variables and nonsymmetrical continuous variables were conducted using the Kruskal-Wallis test.

	All infants	Non-PreE	PreE	*P*
Number of infants	**775**	**581**	**194**	
1-minute Apgar score	8 (6-8)	8 (6-8)	8 (6-8)	**0.46**
5-minute Apgar score	9 (8-9)	9 (8-9)	9 (8-9)	**0.89**
Intrauterine growth restriction	6.30%	4.10%	12.90%	**<0.0001**
Hypoglycemia	19.90%	17.40%	27.30%	**0.0034**
Thrombocytopenia	20.10%	17.20%	28.90%	**0.0006**
Intraventricular hemorrhage	3.20%	3.10%	3.60%	0.73
Bronchopulmonary dysplasia	8.00%	7.80%	8.8$	0.65
Necrotizing enterocolitis	1.60%	1.60%	1.60%	0.99
Mortality	2.30%	2.20%	2.60%	0.74
Length of stay (days, mean ±SD)	17 (±33)	16 (±35)	21 (±24)	**<0.0001**

Table 2: Clinical characteristics and comorbidities of infants admitted to the neonatal intensive care unit.

Data shown as median (IQR) unless otherwise indicated; bivariate analysis, comparisons for non-ordinal categorical measures were conducted using $\chi 2$ or Fisher exact test, which comparisons for ordinal categorical variables and nonsymmetrical continuous variables were conducted using the Kruskal-Wallis test.

	Odds Ratio (95% CI)	*P*
Intrauterine growth restriction	3.421 (1.9, 6.1)	<0.0001
Birth weight, grams	0.999 (0.9, 1.0)	<0.0001
Gestational age, weeks	0.89 (0.8, 0.9)	<0.0001
Hypoglycemia	1.78 (1.2, 2.6)	0.003
Thrombocytopenia	1.94 (1.3, 2.8)	0.0005
Length of stay, days	1.0 (0.9, 1.0)	<0.0001

Table 3: Multi-variable logistic regression analysis to examine comorbidities in infants admitted to the neonatal intensive care unit associated with maternal preeclampsia.

Discussion

Although much still remains unknown, some of the detrimental short-term and long-term effects of preeclampsia on both mother and infant have been described in literature. Recent studies suggest mothers with preeclampsia have an increased risk of developing future

cardiovascular disease, cerebrovascular disease, and end stage renal disease [1]. In agreement with the current study, these mothers also have an increased risk of cesarean section delivery as well as premature delivery due to the complication associated with preeclampsia [6,7]. Although delivery via cesarean section versus induction labor remains controversial, Kawakita et al., reported that induction of labor decreases maternal complications such as maternal intensive care unit admission, birth injury, hemorrhage, and neonatal complications such as Respiratory Distress Syndrome (RDS) and neonatal intensive care unit admission [7]. The current study focused on neonatal outcomes born to pre-eclamptic mothers as well as developmental outcomes at two years of age. The authors observed that preeclampsia increased neonatal morbidities, including but not limited to premature birth associated with increased length of stay, intrauterine growth restriction, hypoglycemia, and thrombocytopenia (seen in first 72 hours of life and resolved by day 10 of life) likely associated with inflammatory changes in placental tissue causing placental hypoperfusion. Furthermore, it was noted there is a significantly increased risk of generalized developmental delay as well as motor delay in neonates born to pre-eclamptic mothers, though the causation of this association remains unknown.

	All infants	Non-PreE	PreE	*P*
Neurodevelopmental delay	**2858**	**2412**	**446**	
Developmental delay	6.6%	6.0%	9.9%	**0.0023**
Speech delay	14.4%	13.6%	18.6%	**0.0056**
Motor delay	3.1%	3.0%	3.8%	0.36
Behavioral delay	2.3%	2.5%	1.6%	0.24

Table 4: Developmental delays at 2 years of age in infants born to mothers with and without preeclampsia.

*Removed infants that died prior to 2 years of age; bivariate analysis, comparisons for non-ordinal categorical measures were conducted using χ^2 or Fisher exact test.

Preeclampsia creates a chronic stressful environment, which, in theory, could increase the fetal cortisol levels that allows for lung maturity. As Rugolo and colleagues suggested in their review article, infants born to pre-eclamptic mothers reportedly have lower incidence of RDS in neonates born prior to 34 weeks in contrast with neonates born prior to 32 weeks. However, the number of admissions to the neonatal intensive care unit for late preterm infants affected by maternal pre-eclampsia it did not change due to other associated morbidities [4]. Several additional studies have shown increased incidence of RDS and mortality in infants born to mothers with preeclampsia, especially when these infants must be delivered immediately [5,8-10]. Pre-eclamptic mothers have increased levels of soluble vascular endothelial growth factor receptor-1, which impairs important vascular endothelial growth factor receptor signaling for pulmonary development and explains the increased risk for respiratory complications and morbidity [3,4,11]. Due to these factors, preeclampsia may also increase the risk of bronchopulmonary dysplasia; however, this increased risk was not evident in the current study [4].

Preeclampsia is a known risk factor for necrotizing enterocolitis [12,13]. However, in the current study, there were no significant differences in rates of necrotizing enterocolitis based on pre-eclamptic status, which is consistent with findings by Rugolo and colleagues [4]. Additional short-term outcomes that may be associated with preeclampsia include neutropenia, sepsis, feeding problems, and encephalopathy; however, these comorbidities were not examined in the present study.

Multiple studies conducted in the past decade have established impairments in verbal abilities, cognitive developmental delay, and behavior issues such as autism spectrum disorders in infants born to pre-eclamptic mothers; this is supported by the current study's findings of nearly 80% of neonates in the preeclampsia group having at least one type of developmental delay at follow-up [4,9]. Multiple mechanisms that affect the neonatal brain during second and third trimesters in pregnancy of pre-eclamptic mother have been identified. Neerhof et al., discovered that during embryogenesis there is suboptimal utero-placental perfusion arising from abnormal trophoblast differentiation and effects of vascular compromise progress at a variable rate during all three trimesters, possibly giving rise to neonatal developmental delay [14]. Walker et al., also noted abnormal trophoblast bilayer folding associated with neonatal developmental delay and/or autism spectrum disorder in infants born to pre-eclamptic mothers [15].

Several studies have also identified common biomarkers involved with pro-inflammatory or inflammatory state in preeclampsia are associated with neonatal developmental delays such as IFN-Ɣ, IL-4, IL-5 etc. Despite these studies suggesting association of preeclampsia and neonatal developmental delays, the subject remains controversial and further research is needed to conclude that there is a robust link between preeclampsia and neurodevelopmental delay. Many long-term adverse effects of preeclampsia on infants have not been well studied. These long-term outcomes may include neurologic alterations, mental health illnesses, and increased risk of hospitalization for metabolic, nutritional, endocrine, and hematologic diseases [4,10]. We did not examine these outcomes in the present study, but it is an important area of future research.

This study was limited by the relatively short duration of follow-up. It is likely that more of these infants will develop some type of neurodevelopmental disorder later in childhood. Future research is planned to allow for a longer duration of follow-up and to examine a broader range of outcomes.

Conclusion

Maternal preeclampsia increases the risk of having a multiple gestation pregnancy, delivering an infant via cesarean section, and having a preterm birth. Infants born to pre-eclamptic mothers also have an increased risk of having a longer neonatal hospital length of stay as well as developing hypoglycemia and thrombocytopenia. Preeclampsia increases the risk of developmental delay in early childhood. Additional studies are warranted with longer follow-up to further assess neurodevelopmental delays as well as behavioral issues associated with preeclampsia in mothers.

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