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Hematologic Effects of Placental Pathology on Very Low Birthweight (VLBW) Infants Born to Mothers with Preeclampsia

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Running Title: Placental Effects in Preeclampsia

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Condensation

Infants born to mothers with preeclampsia who had neutropenia and thrombocytopenia did not have an increased occurrence of placental infarction or maternal vasculopathy but were more likely to be small for gestational age (SGA) and of lower gestational age.

Abstract

Objective: To investigate the effect of placental pathology on neonatal white blood cells (wbc), platelets (plt), hematocrit (hct) and nucleated red blood cells (nrbc) in very low birthweight (VLBW) infants born to mothers with preeclampsia.

Study Design: Retrospective cohort study of infants with birthweight <1500g born to mothers with preeclampsia from 7/2002-7/2006 at a single level 3 NICU. Placental pathology was reviewed for presence placental infarction and vasculopathy. Hematologic parameters from day of life 0, 1, and 2 were obtained. Statistical analysis included repeated measures ANOVA and multivariable analysis using logistic regression.

Results: The study sample included 203 infants with EGA of 28 ± 3 weeks; 45% had placental infarctions and 26% placental vasculopathy. Infants with neutropenia and thrombocytopenia did not have an increased occurrence of placental infarction or maternal vasculopathy but were more likely to be SGA and of lower gestational age compared to infants without neutropenia or thrombocytopenia. After multivariable analysis,

gestational age and SGA remained associated with both neutropenia and thrombocytopenia while placental infarction and vasculopathy did not remain in the models.

Conclusions: In our population of VLBW infants born to mothers with preeclampsia, placental pathology was common. There was no association of placental infarction or vasculopathy with neonatal neutropenia, thrombocytopenia. The data suggest that neonatal hematologic effects of maternal preeclampsia, if related to placental insufficiency, are associated with factors other than placental histology.

Key words: placenta, placental insufficiency, neonatal thrombocytopenia and neutropenia

Introduction

Preeclampsia is a common disorder of pregnancy affecting nearly 5-8% of pregnant women annually in the United States. The NIH reported in the year 2000 that preeclampsia had risen by one-third over the previous decade[1]. Preeclampsia is known to be a common cause of neonatal neutropenia and thrombocytopenia. It has previously been postulated that both neonatal neutropenia and thrombocytopenia result from decreased production of white blood cells and platelets from placental insufficiency [2-9].

Preeclampsia is also known to have associated placental pathology [10]. Different placental histopathologies are associated with specific clinical features of preterm preeclampsia. Severe maternal proteinuria is related to placental chronic inflammation, while lower maternal antepartum platelet counts are related to placental abruption and infarction. Lower birthweight percentiles and lighter placentas are directly associated with uteroplacental vascular lesions [11].

To date, the link between different placental pathological conditions associated with preeclampsia and neonatal neutropenia and thrombocytopenia have not been explored. In this study, we hypothesized that there would be specific placental findings associated with neonatal hematologic abnormalities in infants born to mothers with preeclampsia.

The purpose of this study was to investigate the association between placental pathology and neonatal white blood cells (wbc), platelets (plt), hematocrit (hct) and nucleated red blood cells (nrbc) in VLBW infants born to mothers with preeclampsia.

Methods

The study was a retrospective nested-cohort study of VLBW infants (<1500gm) born to mothers with preeclampsia at Christiana Care Health System. Christiana Care Health System is the single level 3 regional NICU serving the state of Delaware. The study sample included inborn infants cared for between July 2002 and July 2006. The study sample included only infants born to mothers with preeclampsia.

The diagnosis of preeclampsia was made by the attending obstetrician based on ACOG guidelines of elevated blood pressure (>140 systolic or >90 diastolic) and proteinuria (>0.3gm of protein in a 24 hour urine collection) after 20 weeks of gestation [12]. For the purposes of this study, estimated gestational age (EGA) was defined by best obstetric estimate. Small for gestational age (SGA) was defined as birth weight <10%. Data on prenatal steroid administration was collected and mothers were classified as receiving antenatal steroids if they received a minimum of 1 dose of betamethasone or dexamethasone prior to delivery.

Clinical pathology reports were obtained on all infants. The decision to send the placenta for pathologic evaluation was made by the attending obstetrician. The placentas were examined by one of nine attending pathologists at Christiana Health Care System who were blinded to the clinical and hematologic outcomes of the infants. The placentas were systematically reviewed according to the Placental Pathology Practice Guideline Development Task Force [13]. The reports were reviewed for placental abnormalities using standard definitions for commonly described placental lesions [14]. All the infants included in this study had placental reports. Those born to mothers with preeclampsia who did not have a placental pathology report were excluded from this study.

Infants in the study sample had complete blood counts (cbc) drawn as per NICU protocol. This included a cbc on admission and the 1st two days of life. Cbc's were obtained more frequently as clinically indicated. Hematologic parameters investigated included total white blood cell count, platelet count, hematocrit, and total nucleated red blood cells. All cbc's were analyzed in standard fashion using a Coulter Counter (Hialiah, FL). Total nucleated red blood cells were calculated by multiplying the total WBC count by the number of NRBC counted per 100 WBC. .

Thrombocytopenia was defined as platelet count less than $100K/mm^3$ [15]. Neutropenia was defined by Mouzhino criteria: absolute neutrophil count (ANC) less than 500 on day of life 0, ANC less than 2000 on day of life 1, and ANC less than 1100 on day of life 2 [16].

Statistics

Statistical analysis included both univariable and multivariable analysis. Univariable analysis included Chi Square, Mann-Whitney U test, ANOVA, and repeated measures ANOVA as appropriate. Multivariable analysis includes Logistic Regression. A p value $<.05$ was considered significant; all data are expressed as mean ± SD.

Results

During the study period, 211inborn infants were born to mothers with preeclampsia. The final study sample included 203 infants; 8 infants born to mother with preeclampsia were excluded as they did not have placental pathology results. In the study sample, 30 infants were diagnosed with neutropenia and 48 infants with thrombocytopenia during the 1st 48 hours of life. The distribution of the placental pathologies included: infarction (45%), maternal vasculopathy (26%), meconium staining (16%), histologic chorioamnionitis (13%), calcification (9%) and funisitis (3%). Due to their prevalence, placental infarction, maternal vasculopathy and placental calcifications were chosen to compare to the presence or absence of neutropenia and thrombocytopenia, total nucleated red blood cells and hematocrit values. Histologic chorioamnionitis was not considered in relationship to neonatal parameters as it was uncommon and likely not related to maternal preeclampsia but rather other co-morbid factors.

Infants with neutropenia were of lower gestation, lower birth weight and more likely to be SGA compared to the infants without neutropenia (Table 1). There were no differences in the occurrence of placental

infarction, placental vasculopathy or placental weight in the infants with neutropenia compared to those without neutropenia. After multivariable analysis to control for potential confounding variables including: gestational age, birthweight, race, SGA, multiple gestation, use of prenatal steroids, and placental pathology, only gestational age (odds ratio of 1.3, 95% confidence 1.1-1.6) and SGA (odds ratio of 4.2 (CI 1.3-13.5) remained associated with neutropenia. Neither placental weight nor the presence of placental infarction, calcification or vasculopathy was associated with neonatal neutropenia.

Similarly, infants with thrombocytopenia were also found to be of lower gestational age, birth weight and more likely to be SGA. Again, there were no differences found in the occurrence of placental infarction, placental vasculopathy, calcification, or placental weight when compared to the infants without thrombocytopenia (Table 2). After multivariable analysis to control for potential confounding variables including: gestational age, birthweight, SGA, multiple gestation, use of prenatal steroids and placental pathology, only gestational age (OR 1.2 , 95% CI 1.0-1.4) and SGA (OR 4.2, CI 1.6-11) were associated with an increased odds of thrombocytopenia. Neither placental weight nor the presence of placental infarction, calcification, or vasculopathy was associated with neonatal neutropenia.

No association was found between the presence of placental infarction, placental calcification or placental vasculopathies and hematocrit or nucleated red blood cells in the first 48 hours of life (data not shown).

Discussion

In our population of VLBW infants born to mothers with preeclampsia, placental pathology was common. Despite the common occurrence of placental infarction and maternal vasculopathy, these findings were not associated with neonatal neutropenia or thrombocytopenia. After controlling for potential confounding variables lower birthweight, lower gestational age, and/or SGA remained associated with an increased odds of neonatal thrombocytopenia and neutropenia.

Preeclampsia continues to be an increasing problem associated with preterm birth and is known to be a common cause of neonatal neutropenia and thrombocytopenia [1]. The incidence of neutropenia is reported as high as 49% in pregnancy induced hypertension exposed infants [2]. Consistent with our findings, neutropenia severity has been correlated with the severity of growth restriction and prematurity [4]. Kinetic investigations have suggested that neutropenia in infants born to mothers with preeclampsia is secondary to decreased production of white blood cells as evidenced by decreased circulating, marginated, storage, progenitor and proliferative neutrophils [2]. Our data suggest that the decreased production of white blood

cells is not associated with histologic changes in the placenta including placental infarction or vasculopathy.

Early onset neonatal thrombocytopenia is most commonly observed secondary to placental insufficiency with maternal hypertension being the biggest risk factor [17]. Burrows and colleagues found that in hypertensive mothers, preterm birth was the major risk factor for neonatal thrombocytopenia. Term infants exposed to maternal hypertension had the same incidence of thrombocytopenia as the control population [5]. This finding suggests that hypertension effects may be of a different pathophysiologic pathway in term versus preterm infants. This observation is consistent with our finding of thrombocytopenia associated with lower gestational age in infants born to mothers with preeclampsia.

Preelcampsia is known to have associated placental pathology. Redline et al evaluated 609 placentas and found most placental lesions prior to 37 weeks gestation, specifically maternal vasculopathy, villitis and increased intervillous fibrin were increased in pregnancies complicated by hypertension [18]. Soma et al described that there are many microscopic findings common in the placentas of hypertensive patients. These lesions included increased syncytial knots, villi hypovascularity, cytotrophoblastic proliferation, with thickened basement membranes, atherosis of the spiral arteries and narrowed fetal capillaries [10]. Different placental histopathologies have been associated with specific clinical features of preterm preeclampsia. Severe maternal proteinuria has been related to placental chronic inflammation, while lower maternal antepartum platelet counts were related to placental abruption and infarction. In addition, lower birthweight percentiles and lighter placentas were directly associated to uteroplacental vascular lesions [19]. Ghidini's prospective study used a scoring system based on severity and extent of placental vascular and villous lesions and found that the clinical diagnosis of preeclampsia increased with progressive uteroplacental impairment [11]. The lesions defined in Ghidini's study were analyzed for more specific lesions than is typically found in a standard placental pathology report and could not be applied to this study.

We were unable to show any association between placental pathology and neonatal hematologic abnormalities. There are a number of potential explanations for this finding and our data should be

interpreted with caution. There may be no causal effect of placental pathology on neonatal neutropenia or thrombocytopenia. Alternatively, placental pathology may still be associated with the hematologic effects of maternal preeclampsia, however the placental pathologies leading to neutropenia or thrombocytopenia may be different than those selected in this study. As our investigation was retrospective, we may have missed some frequent subtle placental pathologies which may not have been routinely reported on clinical pathology reports. Findings such as increased amounts of syncytial knots and necrosis, thickened trophoblastic basement membranes, and narrowed fetal capillaries as previously discussed findings in preeclamptic placentas tend to be subtle variations that are not typically commented upon in a routine placental pathology analysis. In addition, some frequent findings in preeclampsia, such as meconium staining may be too nonspecific to draw reliable conclusions from. It may be of benefit to form a prospective study designed to have evaluations for specific placental lesions and then analyze if these lesions have direct hematologic correlation.

It is plausible that the placental pathologies we investigated were not necessarily associated with physiologic placental insufficiency. Perhaps other placental factors may be the causative agents of neonatal hematologic aberrations. Histologic chorioamnionitis, common in preterm birth, has been associated with increased levels of cord blood cytokines and increase intracranial hemorrhage in neonates [20-21]. Inflammation may have a contributing role and warrant further investigation in regards to preeclampsia and neonatal neutropenia and thrombocytopenia. The number of infants born to mothers with histologic chorioamnionitis in our study cohort was too small to make a meaningful association in our study. Furthermore, histologic chorioamnionitis may have been associated with other co-morbidities such as premature labor. Other limitations of our study may include the possibility of inter-observer variance and lack of consensus on the diagnosis of placental lesions. However, adhering to methodical practice guidelines at a single institution and standard definitions likely limited this variablity.

In conclusion, in our population of VLBW infants born to mothers with preeclampsia, placental pathology was common. There was however no association of placental infarction or vasculopathy with neonatal

neutropenia, thrombocytopenia, or other hematologic parameters. Our data suggests that the neonatal hematologic effects of maternal preeclampsia, if related to placental insufficiency, are associated with factors other than placental histology.

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Table 1: Univariate Analysis of Neutropenia and Placental Pathologies, EGA, BW, Race, SGA, Multiple Gestation, Prenatal Steroids

	Neutropenia present, n=30	Neutropenia absent, n=173	p
EGA (weeks)	27.9 ± 2.1	29.3 ± 2.4	.02
BW (grams)	852 ± 283	1091 ±267	<.01
Placental Infarction	33%	46%	.20
Placental Calcification	10%	9%	.85
Maternal Vasculopathy	33%	25%	.41
Placental Weight (grams)	217 ± 37	245 ± 85	.17
Race (Caucasian/African American)	31%/68%	50%/40%	.02
SGA	37%	15%	.01
Multiple Gestation	17%	16%	.93
Antenatal Steroids	83%	82%	.9

Table 2: Univariate Analysis of Thrombocytopenia and Placental Pathologies, EGA, BW, Race, SGA, Multiple Gestation, Prenatal Steroids

	Thrombocytopenia present, n=48	Thrombocytopenia absent, n=155	p value
EGA	28.3 ± 3	29.2 ± 2.3	.04
BW	882 ± 327	1073 ± 253	<.01
Placental Infarction	50%	44%	.47
Placental Calcification	10%	8%	.80
Maternal Vasculopathy	25%	28%	.73
Placental Weight (grams)	231 ± 130	223 ± 70	.87
Race (Caucasian/African American)	37%/50%	54%/41%	.06
SGA	43%	17%	<.01
Multiple Gestation	14%	18%	.53
Steroids	68%	69%	.84