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Labor therapeutics and BMI as risk factors for postpartum preeclampsia: a case-control study

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Abstract

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Objectives—This study aims at identifying associations between therapeutics used during labor and the occurrence of postpartum preeclampsia (PPPE), a poorly understood entity.

Study Design and Main Outcome Measures—This is a case-control study of women who received an ICD-9 code for PPPE (cases) during the years 2009–2011, compared to women with a normotensive term pregnancy, delivery and postpartum period until discharge (controls), matched on age (± 1 year) and delivery date (± 3 months). Cases were defined as women having a normotensive term pregnancy, delivery and initial postpartum period (48 hrs post-delivery) but developing hypertension between 48 hrs and 6 weeks postpartum. Single variable and multiple variable models were used to determine significant risk factors.

Results—Forty-three women with PPPE were compared to 86 controls. Use of vasopressors and oxytocin did not differ between cases and controls, but rate of fluids administered during labor (OR= 1.68 per 100cc/h; 95% CI: 1.09–2.59, $p=0.02$) and an elevated pre-pregnancy/first trimester BMI (OR=1.18 per kg/m^2 , 95% CI: 1.07–1.3, $p=0.001$) were identified as significant risk factors in multivariate analysis.

Conclusions—We identified two potentially modifiable risk factors for PPPE; further studies are needed to better define the role of these two variables in the development of PPPE.

Keywords

postpartum preeclampsia; BMI; fluids; labor therapeutics; obesity

INTRODUCTION

Preeclampsia, a significant source of maternal morbidity and mortality, is defined as the onset of new hypertension after 20 weeks of gestation with associated proteinuria and/or multisystemic dysfunction. It complicates 3 to 5% of the pregnancies in the United States [1]. While the pathophysiology is not completely understood, preeclampsia has been linked to abnormal trophoblastic function and maternal microvascular disease [2, 3]. There is no specific treatment for preeclampsia, except delivery of the fetus and placenta [1].

Often preeclampsia occurs during the prenatal course, either in the setting of normotension or preexisting chronic hypertension. Sometimes, preeclampsia can first manifest in the postpartum period, either after a pregnancy complicated by gestational hypertension, preexisting hypertension, or more rarely after a normotensive pregnancy [4–13]. Postpartum preeclampsia (PPPE) has been most commonly defined in the literature as a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg on at least two occasions, 4h apart and presenting more than 48h after delivery and before 6 weeks postpartum, without the need of a proteinuria [6–8, 11, 14, 15]. The majority of studies of PPPE include women with pregnancies complicated by hypertension or preeclampsia [6–8]. A study of PPPE after normotensive pregnancy found that advanced maternal age (> 40 years old), Hispanic ethnicity, Black race, obesity and a history of gestational diabetes during the index pregnancy are risk factors for PPPE [11]. We were interested in risk factors for PPPE following a normotensive pregnancy and hypothesized that therapeutics used during labor, such as fluids, oxytocin or the type of anesthesia used during labor, may be risk factors for PPPE.

METHODS

Study population

Our retrospective study was conducted at Brigham and Women's Hospital (BWH) (Boston, MA) using cases of PPPE and controls identified through an administrative dataset, the Research Patient Data Registry (RPDR), a centralized database from Partners Healthcare system. We obtained lists of all women with ICD9 codes associated with postpartum preeclampsia (642.XX) and lists of women receiving an ICD9 code of normal delivery (650) at admission for their delivery between January 1st 2009 and December 31st 2011. We excluded women that carried codes associated with complications at delivery.

This study received approval from the Institutional Review Board. Data were abstracted from medical charts. Subjects with incomplete medical records were excluded. Once an ICD9 code identified a possible case of PPPE, the medical record was reviewed to confirm the following: the normotensive delivery of a live child at term (>37 weeks) after a normotensive pregnancy and a normotensive interval during the first 48hrs postpartum with the first development of hypertension, defined as SBP \geq 140 mmHg and/or DBP \geq 90 mmHg, 48 hrs to 6 weeks after delivery. To qualify, there had to be two elevated blood pressures at least 4hrs apart or one elevated blood pressure with the initiation of an antihypertensive medication or at least two elevated blood pressures in the severe range (SBP \geq 160 mm Hg and/or DBP \geq 110 mm Hg) over any time interval. Term delivery was required to reduce the right truncation bias that would have been implied by the inclusion of pregnancies that ended preterm.

Normotensive pregnancy was defined when subjects maintained SBP <140 mmHg, and DBP <90 mmHg throughout pregnancy and without mention of chronic hypertension in the medical chart before the pregnancy. Elevated blood pressures occurring only during labor did not exclude subject unless they persisted for more than six hours.

Two controls were chosen randomly from the list of women with normal delivery code at admission. Controls were matched to each case on maternal age (\pm 1 year) and date of delivery (\pm 3 months), with the same inclusion and exclusion criteria as well as normotension until discharge.

Therapeutics used during labor such as total volume of fluids infused, neuraxial anesthesia (spinal, epidural or spinal-epidural combined) administered, and use of oxytocin were abstracted from the medical record. Length of time on labor and delivery unit was calculated as the difference between the recorded time of admission on the labor and delivery floor for delivery to the recorded time of the patient's transfer to the postpartum floor for all the subjects as it was the time when most of the fluids were received by the subjects. The length of time on labor and delivery unit and the volume of fluids infused allowed calculation of the rate of infusion (total volume/length of time on labor and delivery unit). Demographic characteristics included: maternal age at delivery, race, height, early pregnancy weight (defined as self-reported weight before pregnancy as documented in the medical record at the first prenatal visit or measured weight during the first 12 weeks of pregnancy), self-reported weight at delivery, and gestational age at delivery. BMI was calculated and reported

as early pregnancy BMI. Gestational weight gain was also calculated. Placental retention was defined by the need of a manual extraction in the immediate postpartum period [16] or by the need for dilation and curettage (D&C) in the first 6 weeks postpartum. Review of the discharge summary indicated if non-steroidal anti-inflammatory were prescribed. In addition, review of the medical records was done for the controls to ensure that these women were not readmitted for PPPE during the 6 weeks following discharge. For cases of PPPE, time since delivery at presentation, symptoms at presentation, highest blood pressures recorded and laboratory testing results were also abstracted. The first author (GS) abstracted all the charts and entered all the data. All cases of PPPE were validated by two authors (GS and EWS).

Statistical analysis

Conditional logistic regression to predict de novo PPPE was conducted incorporating the case-control matching by stratification. Odds ratios and 95% confidence intervals were reported. A multiple variable model was derived using a combination of stepwise algorithms and investigator-directed modeling while considering collinearity of potential predictors, retaining variables with $p < 0.15$. There was missing data for some variables in the full model, therefore the final model was recalculated to maximize the sample size and retain predictors with $p < 0.10$ [17]. SAS version 9.4 was used. Smoking status, history of gestational diabetes/type 2 diabetes or use of ergot derivative were not included in the analysis due to the small number of exposed subjects.

RESULTS

A total of 296 cases with an admission ICD9 code of postpartum preeclampsia were identified during the study period out of 21,384 total deliveries. Of these, 43 cases met our study criteria for PPPE. Reasons for exclusion included a prior diagnosis of gestational hypertension and/or preeclampsia during the pregnancy ($n=163$), the development of sustained hypertension during the labor or hypertension within 48hrs of delivery ($n=21$), a diagnosis of chronic hypertension ($n=28$), or because of a delivery before 37 weeks ($n=9$). Cases were also excluded if documentation of normotension during the pregnancy and/or the postpartum period was insufficient ($n = 21$), if there were incomplete postpartum records for a diagnosis of PPPE ($n = 2$), if admission was refused resulting in incomplete data ($n=1$), if the diagnosis occurred after 6 weeks postpartum ($n=1$) and if blood pressure values were below the study threshold ($n=3$). An additional four women were excluded because the assigned ICD9 code was incorrect. Eighty-six controls satisfied the inclusion criteria and were matched to 43 cases on a two-to-one basis.

Results

Clinical characteristics of the cases and controls are presented in Table 1. Women who developed PPPE had a mean early pregnancy BMI of 30 kg/m^2 ($SD \pm 6$) and a mean gestational weight gain of 23 lbs. ($SD \pm 18$). Cases were more likely to be multiparous (74% of them were multiparous, compared to 49% of the controls). Five cases reported active smoking during their pregnancy. In contrast, controls had a mean early pregnancy BMI of 24.4 kg/m^2 ($SD \pm 6.2$) and a mean gestational weight gain of 28 lbs. ($SD \pm 12$). Gestational

weight gain was not statistically different in the two groups ($p=0.09$). There were 2 women with gestational diabetes in the PPPE group versus 5 in the control group; in addition, one woman in each group had type 2 diabetes. One woman in the case group went through in vitro fertilization (IVF) and four in the control group.

Characteristics of labor, use of neuraxial anesthesia, the therapeutics received during labor are described in Table 2. Oxytocin use during labor was common and not different between cases and controls. Neuraxial anesthesia was common and there was no significant difference between cases and controls. The cesarean delivery rate was significantly higher in cases versus controls in univariate analysis. Fluids infused while being on labor and delivery unit included Ringer's lactate solution for volume management and 0.9% saline for administration of medications (e.g. oxytocin). In the PPPE group, 30% (13/43) of women received either ephedrine or phenylephrine for vasopressors support compared with 34% (29/86) in the control group ($p=0.8$). In the first two hours postpartum, one woman in the case group, and two in the control group, received an ergot derivative to help control uterine tonus. Only one woman in the PPPE group, following a delivery by cesarean delivery, and no women in the control group received a blood transfusion. None of the women in the case group needed a manual extraction or D&C for placental retention, and two in the control group underwent D&C for placental retention.

There was no significant difference in the sex of the baby between the two groups. At discharge, the proportion of women receiving a recommendation for NSAIDs was not significantly different between the groups (79% in the case group versus 83% in the control group, $p=0.46$).

Table 1 and 2 show also the association of single variables with PPPE. Black race, higher parity, occurrence of cesarean delivery, and higher early pregnancy BMI were significantly associated with PPPE (all $p < 0.01$). The rate of fluid administration while on labor and delivery unit was of borderline significance ($p=0.07$).

Table displays multiple variable logistic regression modeling controlling for parity, c-section, early pregnancy BMI, rate of fluids and Black race. In this analysis, rate of fluid administration (OR= 1.68 per 100cc/h; 95% CI: 1.09–2.59, $p=0.02$) and early pregnancy BMI (OR=1.18 per kg/m^2 , 95% CI: 1.07–1.3, $p=0.001$) were significant risk factors for the onset of PPPE.

Clinical characteristics of the 43 women at presentation for PPPE are shown in Table 4. Women were 10 ± 6 days postpartum on average when they presented with PPPE, with 8 women presenting more than 15 days postpartum. Two women were already hospitalized when they were diagnosed with PPPE (one was 2 days postpartum; the other was re-hospitalized for a methicillin-resistant *Staphylococcus aureus* infection at 2 weeks postpartum and developed hypertension on her 19th day postpartum). The other 41 women were readmitted for PPPE. Eclampsia was the presenting symptom in two women (2/43, 5%). Among women with PPPE, headache was the most common symptom (30/43, 70%), followed by shortness of breath (7/43, 16%) and abdominal pain (5/43, 12%). Two women presented at BWH after having checked their blood pressures and finding them elevated at

their pediatrician office or at home. Six women were asymptomatic and were diagnosed on a routine blood pressure check during a scheduled two-week postnatal visit. The average highest SBP recorded for PPPE was 173 ± 13 mmHg (mean \pm SD) mmHg and the highest DBP was 102 ± 10 (mean \pm SD) mmHg. One woman presented with blood pressures as high as 210/130 mmHg, yet was asymptomatic. Six women had elevated liver enzymes, with three being more than twice the normal values. All of the women had a normal creatinine levels. In 29 women, the ratio of urine protein/urine creatinine was performed; 4 of the 29 (14%) women had a positive (ratio = 0.3) result. No urine dipsticks were ordered.

In the control group, all women were documented as normotensive until discharge, at 56h postpartum (range: 24–190 hrs. Per our protocol criteria, and after review of their medical records, none of these 86 women were readmitted to BWH for PPPE.

DISCUSSION

In this study, we found that the rate of intravenous fluids received on labor and delivery unit and early pregnancy BMI were significant risk factors for PPPE. Black race, parity and mode of delivery significant in univariate were not significant after adjustment. The results are of potential value as both the rate of fluids received on labor and delivery unit and early pregnancy BMI are modifiable risk factors for PPPE.

The risk factor identified in our study of an increased rate of fluids while on labor and delivery unit is a new finding. A possible explanation for this finding is that women who receive greater rate of intravenous crystalloids during labor and delivery may shift more intravenous fluids toward the interstitial compartment [18–21], and may subsequently develop volume overload when the fluid is remobilized with the development of PPPE. This could be related to subclinical alterations in renal function and impaired suppressability of the renin-angiotensin-aldosterone system (RAAS), as described in other populations [22]. Increased vasoconstriction secondary to increased levels of soluble fms-like tyrosine kinase-1 (sFlt1) [23] could also contribute to reduced renal function and impaired ability to clear administered fluids given the recent demonstration of higher sFlt1 levels a few hours prior to cesarean delivery in women who developed PPPE compared to women who remain normotensive [24]. Given that PPPE can develop between 48h and 6 weeks postpartum, it may well be a heterogeneous disorder.

The other factor identified in our study is an increase in early pregnancy BMI. Obesity (BMI ≥ 30 kg/m²) is a recognized risk factor for preeclampsia [1], with BMI at delivery noted to be a specific risk factor for PPPE [11]. We sought to examine the effects of early pregnancy BMI, as late pregnancy BMI may be confounded by fluid retention. Pregnancy weight gain did not appear to be a risk factor for PPPE.

Our results are broadly consistent with those of prior investigations [11, 13]. Using a retrospective case-control study with 34 cases and 68 controls and the same definition of PPPE as our study, Bigelow et al. identified BMI at delivery, age >40 years, a diagnosis of gestational diabetes in the index pregnancy, Black race and Latino ethnicity as risk factors [11]. The incidence of gestational diabetes was low in our series and we did not see a

difference in rates of gestational diabetes. We were unable to evaluate ethnicity, as it is not recorded independently from race in our record system; however, our multivariate analysis did not find race to be a significant risk factor for PPPE, after adjusting for other risk factors.

In a recent retrospective study performed in Japan [13], Takaoka et al. also examined demographic risk factors for PPPE, defined as the onset of hypertension after a normotensive pregnancy, after delivery, including cases occurring within the first 48h postpartum. In this study, pre-pregnancy BMI above 25kg/m², c-section and use of assisted reproductive technologies, presence of chronic nephritis, hypothyroidism and blood pressures (BP) in the high normal range (SBP 130 mm Hg or DBP 85 mm Hg) at the first prenatal visit (before 14 weeks gestation) or before delivery were found to be independent risk factors for PPPE.

In our 43 cases of PPPE, several had serious complications including eclampsia, severe hypertension or elevated liver enzymes (at least twice the normal). As a potentially life-threatening entity [5, 25], the early identification and prevention of PPPE could help decrease maternal postpartum morbidity as well as healthcare costs linked to readmission;

There are several limitations to our study. We have been able to study only women who presented with PPPE at BWH: some of the women in the control group and additional cases may have also developed PPPE and gone for care elsewhere. Although we abstracted discharge recommendations for the use of NSAIDs, we did not have data on the actual use of NSAIDs following discharge. NSAID use may influence the development of PPPE by decreasing renal blood flow and limiting the ability of the women to manage intravascular volume, resulting in an increased risk of PPPE [26, 27]. In addition, robust collection and reporting of urinary output were lacking; this data would assist in the determination of fluid balance in the peri-delivery period. Given the low numbers of women reporting active smoking status during pregnancy, we could not evaluate if smoking was a risk factor for PPPE. Finally, the role of specific anesthetic regimens (spinal, epidural or spinal-epidural combined) could not be explored given the low number of patients receiving each regimen.

Conclusion

We identified increased rate of fluids infused during labor and early pregnancy BMI and as risk factors for PPPE. These data lend weight to existing recommendations [28] to reduce obesity before pregnancy. Further studies are needed to confirm the influence of rate of fluid administration during labor as a risk factor for development of PPPE.

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Highlights

- New mechanisms leading to postpartum preeclampsia are proposed.
- As shown before, we identified pre-pregnancy/first trimester BMI as risk factor.
- We also identified rate of fluids during labor as a new risk factor.

Table 1

Single variable comparison for the clinical characteristics of the PPPE cases and controls

	PPPE cases (n=43)	Controls (n=86)	Odds Ratio (95% CI)	p-value
Mean ± SD				
Age at delivery (year)	32±6	31±6	1.096 (0.765, 1.570)	0.62
Parity	2.3±1.3	1.7±0.9	1.72 (1.16–2.55)	0.007
Pre-pregnancy/first trimester BMI (kg/m ²)	30.0±6.1	24.4±6.2	1.17 (1.07–1.27)	0.0004
Gestational weight gain (lbs)	23±18	28±12	0.98 (0.95–1.00)	0.085
Gestational age at delivery (weeks)	39.2±1	39.5±1	0.77 (0.53–1.14)	0.195
N (%)				
Black Race	16 (37)	11 (13)	4.22 (1.62–11)	0.003
Active smoking status	5 (12)	2 (2)	8.58 (0.98–74.91)	0.052
Gender of the baby (male)	23 (53)	43 (50)	1.2 (0.58–2.48)	0.623

CI: Confidence Interval

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Table 2

Single variable comparison for the therapeutic labor and delivery data of women with PPPE (n=43) and without (n=86) de novo PPPE

Therapeutics and Labor Data				
	PPPE Cases (n=43)	Controls (n=86)	Odds Ratio (95% CI)	p-value
N (%)				
Cesarean delivery	16 (37)	15 (17)	3.175, (1.26–8)	0.01
Use of oxytocin during labor	34 (74)	60 (70)	1.547, (0.68–3.51)	0.30
Use of ergots in postpartum	1 (2)	2 (2)	1 (0.09–11.03)	1.0
Use of vasopressors during labor	13 (30)	30 (35)	1.55, (0.68–3.51)	0.30
Use of neuraxial anesthesia	39 (91)	75 (87)	1.38, (0.44–4.32)	0.58
Mean ± SD				
Total volume infused during labor (ml) (OR for a change of 100 ml)	3116±1517	3142±1347	1, (0.97–1.03)	0.91
Rate of fluids during labor (ml/hr) (OR for a change of 100ml/hr)	306±183	255±123	1.28, (0.98–1.68)	0.07
Length of time in labor and delivery unit (hours)	12.2 (7.5)	14.8 (9)	0.961, (0.92–1.01)	0.11

CI: Confidence Interval

Table 3

Full model and Final multivariable model of variables to predict de novo PPPE

Full model before selection			
Variable	Odds Ratio	95% CI	p-value
Parity	2.13	1.02–4.43	0.04
Black race	1.09	0.34–3.44	0.89
Cesarean delivery	3.18	0.56–18.09	0.19
Pre-pregnancy/first trimester BMI	1.13	1.00–1.28	0.05
Rate fluids/hour (per 100ml/hr)	1.56	0.95–2.54	0.08
Final Model			
Rate fluids/hr (per 100 ml/hr)	1.68	1.09–2.59	0.02
Early pregnancy BMI	1.18	1.07–1.30	0.001

CI: Confidence Interval

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Table 4

Clinical Characteristics of women with de novo PPPE at readmission

Clinical Characteristics of the women with de novo PPPE (n=43)	
Mean \pm SD	
Time before readmission (days)	10 \pm 6
Highest mean systolic blood pressure (mm Hg)	173 \pm 13
Highest mean diastolic blood pressure (mm Hg)	102 \pm 10
N (%)	
Asymptomatic	6 (14)
Symptoms (symptoms could overlap)	
Eclampsia	2 (5)
Headaches	30 (70)
Abdominal/chest pain	10 (23)
Shortness of breath	7 (16)

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