Prenatal Low-Dose Aspirin Use Associated with Reduced Incidence of Postpartum Hypertension among Women with Preeclampsia

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Abstract

Objective Postpartum hypertension (PP-HTN), defined as systolic/diastolic blood pressure (SBP/DBP) ≥140/90, on two occasions at least 4 hours apart after delivery occurs in up to 50% of preeclamptic pregnancies, and is associated with adverse maternal outcomes. Excessive production of antiangiogenic factors (i.e., soluble fms-like tyrosine kinase 1 [sFLT1]) and reduced levels of proangiogenic factors (i.e., placental growth factor [PlGF]) are associated with preeclamptic pregnancies. The aim of this study was to identify clinical risk factors and/or serum biomarkers associated with PP-HTN in preeclampsia.

Study Design Preeclamptic women ($n = 82$, aged ≥18 years) were prospectively enrolled in an observational study. Serial blood pressures were obtained through the labor course and until 48 hours postpartum, and serum was obtained within 24 hours postpartum. Statistical analysis was performed by using Student's two-tailed *t*-test and Fisher's exact test.

Results Baseline comorbidities and antihypertensive use were similar among those who developed PP-HTN and those who did not. Among preeclamptic patients, 33% developed PP-HTN; these had significantly more severe preeclampsia features versus no PP-HTN (96 vs. 78%, $p = 0.05$). PP-HTN was associated with higher re-hospitalization rates (26 vs. 6%, $p = 0.01$). Among those taking low-dose aspirin (ASA) for preeclampsia prophylaxis ($n = 12$), PP-HTN was significantly less frequent versus those not taking low-dose ASA (0 vs. 22%, $p = 0.007$). Low-dose ASA use was associated with significantly lower peripartum sFLT1 levels (4,650 ± 2,335 vs. 7,870 ± 6,282 pg/mL, $p = 0.03$) and sFLT1/PlGF ratio (397 ± 196 vs. 1,527 ± 2,668, $p = 0.03$).

Conclusion One-third of women with preeclampsia develop PP-HTN; these patients have more severe preeclampsia and have higher re-hospitalization rates. Prenatal low-

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dose ASA use was associated with significantly lower incidence of PP-HTN, reduced levels of antiangiogenic factors, and lower 6-week re-hospitalization rates. These findings, if replicated, may have clinical implications on the use of low-dose ASA during pregnancy to reduce incidence of postpartum HTN.

Key Points

- Postpartum hypertension is common in preeclampsia.
- Prenatal aspirin may reduce postpartum hypertension.
- Prenatal aspirin may reduce sFLT1 levels.

Preeclampsia is a syndrome of pregnancy characterized by new-onset hypertension, proteinuria, and end-organ dysfunction that affects 5 to 10% of pregnancies worldwide.[1–4] In the United States, preeclampsia disproportionately affects African American women, and is also more common in those with underlying cardiovascular risk factors such as hypertension (HTN), obesity, insulin resistance, and hyperlipidemia.[5–8] Preeclampsia is associated with significant short- and long-term cardiovascular and cerebrovascular morbidity, including HTN which may persist for the first week postpartum in up to 50% of preeclamptic pregnancies.[3,4,9] Long-term all-cause mortality is also increased in those with a history of preeclampsia, associated with a 2.2-fold increased risk of death from ischemic heart disease.[10] Patients with history of preeclampsia, chronic HTN, type 1 or 2 diabetes mellitus, obesity, and renal disease are considered moderate to high risk for the development of preeclampsia and current guidelines recommend use of daily low-dose ASA (81 mg per day) prophylaxis during pregnancy, as it has been shown to reduce the frequency of preeclampsia and adverse pregnancy outcomes by 10 to 20%.[11–13]

Endothelial dysfunction and aberrant vascular regulation play central roles in the pathogenesis of preeclampsia and have been shown to persist for years postpartum, even after adjusting for other traditional cardiovascular risk factors.[14] Dysregulated angiogenesis likely occurs in the setting of placental hypoxia, leading to excessive production of antiangiogenic biomarkers such as soluble fms-like tyrosine kinase 1 (sFLT1) and reduced levels of proangiogenic factors such as placental growth factor (PlGF).[15–18] sFLT1 is an antiangiogenic protein produced predominantly by the placenta, but also by monocytes and endothelial cells.[19,20] sFLT1 is a soluble vascular endothelial growth factor (VEGF) inhibitor, which binds to VEGF and PlGF in the circulation, preventing their interaction with their endothelial receptors.[19] Excessive sFLT1 and deficient PlGF may contribute to endothelial dysfunction and the pathogenesis of preeclampsia and its complications.[21] High sFLT1/PlGF ratio has previously been shown to be both sensitive and specific for identifying women at risk of adverse outcomes in the setting of preeclampsia.[21,22] Low-dose ASA has been shown to decrease placental and endothelial secretion of sFLT1 in vitro,[23,24] indicating that its protective effect during pregnancy may be related to modulation of endothelial dysfunction and increased angiogenesis.

The aim of this study was to identify clinical risk factors including low-dose aspirin (ASA) use and serum biomarkers associated with postpartum hypertension (PP-HTN) in preeclampsia.

Materials and Methods

This was a prospective, observational cohort study of women with preeclampsia admitted to the Labor and Delivery Service between August 2017 and October 2018 at Barnes Jewish Hospital, Washington University Medical Center in St. Louis, MO. The study was approved by the institutional review board at Washington University School of Medicine.

Patient selection. Inclusion criteria were (1) delivery at Barnes Jewish Hospital, (2) age >18 years, and (3) diagnosis of preeclampsia. Exclusion criteria were (1) history of cardiomyopathy or coronary artery disease, (2) unable to give informed consent, or (3) HIV.

Preeclampsia was defined according to American College of Obstetrics and Gynecology criteria: systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg, measured on at least two separate occasions at least 4 hours apart or systolic blood pressure >160 mm Hg or diastolic blood pressure >110 mm Hg confirmed within a short interval (minutes), and (1) proteinuria (>300 mg/24 hours, protein/creatinine ratio greater than or equal to 0.3, or at least 2+ on dipstick urinalysis) or (2) platelet count <100,000, serum creatinine >1.1 or a doubling of serum creatinine, elevated liver transaminases to twice normal concentration, pulmonary edema, and cerebral or visual symptoms.[25] Postpartum HTN was defined as systolic >140 or diastolic >90 mm Hg on two occasions at least 4 hours apart after delivery within the 48 hour study period.

Participants were enrolled either during the third trimester of pregnancy or within 24 hours postpartum. Of the 192 eligible subjects, 82 consented to participate.

Blood pressure monitoring: Using a Corometrics 250cx Series maternal/fetal monitor with DINAMAP SuperSTAT blood pressure technology, serial assessment of blood pressure was measured in single measures every 30 minutes throughout the labor course. Postpartum, blood pressure

Table 1 Baseline characteristics

Variable	Postpartum HTN ($n = 27$)	No postpartum HTN ($n = 55$)	*p*-Value
Age at delivery	26.9 (5.5)	27.7 (5.8)	0.5
Gravidity	2.4 (1.4)	2.5 (1.8)	0.7
BMI at delivery	32.6 (6.5)	35.1 (8.3)	0.2
Race			
White	11 (41)	24 (44)	1
Black	16 (59)	29 (53)	0.6
Asian	0 (0)	1 (2)	1
Other	0 (0)	1 (2)	1
Medical comorbidities			
Chronic hypertension	4 (15)	14 (26)	0.4
Gestational hypertension	5 (19)	3 (6)	0.1
Diabetes mellitus	1 (4)	6 (11)	0.4
Tobacco use	4 (15)	6 (11)	0.9
Preeclampsia severity			0.05
Mild	1 (4)	12 (22)	
Severe/HELLP	26 (96)	43 (78)	
Preeclampsia timing			0.4
Preterm (<37 wk of gestation)	16 (59)	29 (53)	
Term (≥ 37 wk of gestation)	11 (41)	26 (47)	
Antihypertensive medications during pregnancy	1 (4)	8 (15)	0.3
Furosemide	0 (0)	1 (2)	1
β-blocker	1 (4)	5 (9)	0.7
Calcium channel blocker	1 (4)	7 (13)	0.3
Aspirin use during pregnancy	0 (0)	12 (22)	0.007
Peak systolic blood pressure (mm Hg)	163 (19)	173 (24)	0.07
Peak diastolic blood pressure (mm Hg)	101 (13)	101 (16)	1.0
Discharge systolic blood pressure (mm Hg)	135 (12)	133 (11)	0.3
Discharge diastolic blood pressure (mm Hg)	87 (8)	80 (11)	0.002

Abbreviations: BMI, body mass index; HELLP, hemolysis, elevated liver enzymes, low platelet count; HTN, hypertension.

Table 2 Clinical results

Variable	Postpartum HTN ($n = 27$)	No postpartum HTN ($n = 55$)	*p*-Value
Hospital readmission	7 (26)	3 (6)	0.01
Fetal complication	8 (30)	19 (35)	0.8
Antihypertensive medications at discharge	20 (74)	20 (36)	0.002
Furosemide	0 (0)	0 (0)	1
Beta-blocker	3 (11)	6 (11)	1
Calcium channel blocker	19 (70)	19 (35)	0.004
ACE inhibitor	2 (7)	1 (2)	0.3
Angiotensin receptor blocker	0 (0)	0 (0)	1
Aldosterone antagonist	1 (4)	0 (0)	0.3
Other diuretic	2 (7)	2 (4)	0.6

Abbreviations: ACE, angiotensin-converting enzyme; HTN, hypertension.

Table 3 Laboratory results: angiogenic biomarker levels in women taking versus not taking low-dose aspirin

Laboratory values	Low-dose aspirin ($n=10$)	No low-dose aspirin ($n=29$)	p-Value
SFLT1 (pg/ng)	4,650 (2,335)	7,870 (6,282)	0.03
PlGF (pg/ng)	13.8 (7.8)	15.2 (22.0)	0.8
SFLT1/PlGF	137 (196)	1527 (2,668)	0.03

Abbreviations: sFLT1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor.

was obtained every 2 to 4 hours per routine obstetrical care for at least 48 hours after delivery by using Phillips SureSigns VS4 automatic blood pressure cuffs.

Serum biomarkers: Maternal serum was obtained within 24 hours of delivery and analyzed by ELISA for sFLT1 and PlGF using previously established methodology.[26]

Medication use: Pregnancy medications were defined as those currently taken by the patient at the time of admission for labor and delivery. Hospital discharge medications were defined as those prescribed at the time of discharge from the hospital after delivery.

Fetal/obstetric complications: Fetal complications were defined as abruption, chorioamnionitis, intrauterine growth restriction, fetal anomaly including fetal congenital heart defect, oligohydramnios, preterm premature rupture of membranes, and infant mechanical ventilation.

Statistical analysis: Student's two-tailed t-test was used to compare continuous variables between groups, and Fisher's exact test was used to compare categorical variables. We considered a two-tailed p-value of less than 0.05 to be statistically significant.

Results

Of the 192 eligible subjects, 112 declined to participate. Of the 82 women enrolled, 27 (33%) developed PP-HTN. There were no significant differences in age, body mass index (BMI), race, or gravidity at delivery between patients who developed PP-HTN and those who did not (►**Table 1**). The majority were African American (59 vs. 53%, $p=0.6$). There were no significant differences between the groups with regards to chronic medical comorbidities including HTN (15 vs. 26%, $p=0.4$) and type 2 diabetes (4 vs. 11%, $p=0.4$). Though there were numerical differences between groups in terms of antihypertensive medications during pregnancy, this was not statistically significant (4 vs. 15%, $p=0.3$). Preterm preeclampsia was equally common in both groups (59 vs. 53%, $p=0.4$). Percent of women preeclampsia with severe features was higher in those who developed PP-HTN versus those who did not (96 vs. 78%, $p=0.05$).

PP-HTN was significantly less common among women receiving prophylactic low-dose ASA (0 vs. 22%, $p=0.007$). Hospital readmissions were significantly higher among women who developed postpartum HTN (26 vs. 6%, $p=0.01$; ►**Table 2**). No women taking low-dose ASA were readmitted to the hospital within 6 weeks of delivery, compared with 14% of women who did not receive low-dose ASA ($p=0.3$). Women with postpartum HTN were more likely to be on antihypertensive medications at the time of hospital discharge (74 vs. 36%, $p=0.002$), most of whom were on calcium channel blockers (70 vs. 35%, $p=0.004$).

Serum biomarkers: The PP-HTN group exhibited a non-significant higher ratio of sFLT1/PIGF versus no PP-HTN ($2{,}728\pm4{,}232$ vs. 723 ± 798, $p=0.2$). ASA exposure was associated with significantly lower sFLT1 ($4{,}650\pm2{,}335$ vs. $7{,}870\pm6{,}282$ pg/mL, $p=0.03$, ►**Table 3**) and ratio of sFLT1/PlGF (397 ± 196 vs. $1{,}527\pm2{,}668$, $p=0.03$) at delivery. The ratio of sFLT1/PIGF was significantly lower in women with chronic HTN (390 ± 271 vs. $1{,}570\pm2{,}704$, $p=0.03$); sFLT1 levels showed a trend toward lower levels in women with chronic HTN ($4{,}205\pm4{,}502$ vs. $8{,}160\pm5{,}790$, $p=0.05$).

Discussion

The results of the present study demonstrate that among women with preeclampsia who received prenatal ASA for preeclampsia prophylaxis, use was associated with significantly lower incidence of PP-HTN, reduced levels of anti-angiogenic factors, and lower 6-week re-hospitalization rates. The association of prophylactic low-dose ASA in preeclampsia and decreased incidence of PP-HTN suggests that low-dose ASA may have salutary effects even after delivery. This is a novel finding with important clinical implications, given the significant rate of postpartum readmissions for HTN and the contribution of HTN to early postpartum mortality in the United States.[27,28] Notably, low-dose ASA use was associated with a significantly decreased level of sFLT1 and ratio of sFLT1/PIGF compared with those who did not receive low-dose ASA, providing potential mechanistic explanation for these findings. Women who developed PP-HTN also showed a trend toward higher ratio of sFLT1/PIGF than those without postpartum HTN, consistent with prior studies indicating that higher sFLT1/PlGF levels are associated with higher risk of adverse maternal outcomes.[21,22]

sFLT1 has been shown in vitro to induce vasoconstriction and endothelial dysfunction, and induces a syndrome resembling preeclampsia in rats.[29] sFLT1 levels rise during the third trimester of all pregnancies but are markedly elevated in pregnancies complicated by preeclampsia.[15,30,31] Higher levels of sFLT1 have previously been associated with more severe preeclampsia phenotypes.[29] sFLT1 levels then rapidly decline following delivery; however, circulating levels of sFLT1 in preeclampsia patients remain persistently elevated above postpartum levels compared with patients without preeclampsia.[15,30–32] PlGF is a pro-angiogenic factor released from placental syncytiotrophoblast and the endothelium.[33] An imbalance in anti- and pro-angiogenic factors, or elevated sFLT1/PlGF ratio, is thought to contribute to endothelial dysfunction, preeclampsia pathogenesis, and adverse maternal outcomes.[21,22] Therefore, sFLT1 and PlGF appear to play an important pathophysiologic role in the development of preeclampsia, and in the subsequent increased prevalence of PP-HTN and cardiovascular dysfunction.

ASA has been shown in vitro to reduce hypoxia-induced sFLT1 production.[23,24] It has been theorized that this is one mechanism by which it is effective in reducing the incidence of preeclampsia among women who are intermediate to high risk for developing the condition.[23] This study supports prior in vitro work, correlating lower clinical sFLT1 levels and sFLT1/PlGF ratio in women who received prophylactic low-dose ASA who did go on to develop preeclampsia. The clinical benefits and associated laboratory findings shown in this study may be related to attenuated sFLT1-mediated endothelial dysfunction, leading to more rapid resolution of preeclampsia-mediated HTN.

In this cohort, approximately 33% of women with preeclampsia develop PP-HTN. Those with PP-HTN had higher rates of preeclampsia with severe features and higher rehospitalization rates compared with those without PP-HTN. Development of PP-HTN was not affected by any other investigated clinical factors, including maternal age, BMI, race, or history of chronic HTN. PP-HTN is the leading cause for 6-week hospital readmission, as postpartum blood pressure rises and peaks 3 to 6 days after delivery.[27,34–36] Studies have shown that in approximately 50% of hypertensive disorders of pregnancy, a blood pressure >150/100 mm Hg develops on postpartum day 5 and close to 20% have systolic blood pressure >170 mm Hg.[37] Unfortunately, many of these patients are not diagnosed and left undertreated.[38] The postpartum period also a high-risk time for severe morbidity associated with hypertensive disorders of pregnancy, with >40% of cases of eclampsia occurring in the postpartum period and the majority of cases intracranial hemorrhage occurring in the early postpartum period.[38,39] Thus, the findings of this study may have important clinical implications on the use of ASA during pregnancy.

Limitations

The study population was relatively small. As this was an observational study, there was no randomization between groups and confounding may play a role in the results. Additionally, the findings of the study, that ASA showed a reduction in PP-HTN were not expected, and as such represent hypothesis testing for a future study.

Conclusion

One-third of women with preeclampsia develop PP-HTN; these patients more often have severe features and have higher re-hospitalization rates. In contrast, prenatal ASA use was associated with significantly lower prevalence of PP-HTN and decreased 6-week re-hospitalization rates. This likely is mediated by attenuated endothelial dysfunction, as prenatal ASA was associated with reduced levels of antiangiogenic factors. These findings, if replicated, may have clinical implications on the use of low-dose ASA during pregnancy. ASA is known to reduce the frequency of preeclampsia and adverse pregnancy outcomes, but these results indicate it may also be associated with decreased postpartum morbidity in women who develop preeclampsia.

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Conflict of Interest

None declared.

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