Hypertension

Epidemiology and Mechanisms of De Novo and Persistent Hypertension in the Postpartum Period

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Background—The pathophysiology of hypertension in the immediate postpartum period is unclear.

Methods and Results—We studied 988 consecutive women admitted to a tertiary medical center for cesarean section of a singleton pregnancy. The angiogenic factors soluble fms-like tyrosine kinase 1 and placental growth factor, both biomarkers associated with preeclampsia, were measured on antepartum blood samples. We then performed multivariable analyses to determine factors associated with the risk of developing postpartum hypertension. Of the 988 women, 184 women (18.6%) developed postpartum hypertension. Of the 184 women, 77 developed de novo hypertension in the postpartum period, and the remainder had a hypertensive disorder of pregnancy in the antepartum period. A higher body mass index and history of diabetes mellitus were associated with the development of postpartum hypertension. The antepartum ratio of soluble fms-like tyrosine kinase 1 to placental growth factor positively correlated with blood pressures in the postpartum period (highest postpartum systolic blood pressure \( r=0.29, P<0.001 \) and diastolic blood pressure \( r=0.28, P<0.001 \)). Moreover, the highest tertile of the antepartum ratio of soluble fms-like tyrosine kinase 1 to placental growth factor was independently associated with postpartum hypertension (de novo hypertensive group: odds ratio, 2.25; 95% confidence interval, 1.19–4.25; \( P=0.01 \); in the persistent hypertensive group: odds ratio, 2.61; 95% confidence interval, 1.12–6.05; \( P=0.02 \)) in multivariable analysis. Women developing postpartum hypertension had longer hospitalizations than those who remained normotensive (6.5±3.5 versus 5.7±3.4 days; \( P<0.001 \)).

Conclusions—Hypertension in the postpartum period is relatively common and is associated with prolonged hospitalization. Women with postpartum hypertension have clinical risk factors and an antepartum plasma angiogenic profile similar to those found in women with preeclampsia. These data suggest that women with postpartum hypertension may represent a group of women with subclinical or unresolved preeclampsia. (Circulation. 2015;132:1726-1733. DOI: 10.1161/CIRCULATIONAHA.115.015721.)

Key Words: angiogenesis ◼ hypertension ◼ postpartum ◼ pre-eclampsia ◼ pregnancy ◼ receptors, vascular endothelial growth factor.

The hypertensive disorders of pregnancy are a well-recognized cause of maternal morbidity and mortality worldwide. The World Health Organization, in a systematic review of global data, recently identified hypertensive disorders of pregnancy as a dominant cause of maternal death in developing countries, accounting for \( \approx 18\% \) of all maternal deaths worldwide.\(^2\) Even among Western countries, characterized by very low rates of maternal death in the peripartum and postpartum periods, hypertensive disorders of pregnancy remain significantly associated with the future development of maternal hypertension, ischemic heart disease, and stroke.\(^2\)

Editorial see p 1690

Clinical Perspective on p 1733

Development of de novo hypertension in the immediate postpartum period (postpartum hypertension [PPHTN]) is an infrequently studied clinical syndrome. PPHTN is usually defined as hypertension appearing after delivery through...
with collection of additional clinical data such as infant birth weight, maternal estimated blood loss during delivery, sequential postpartum SBP and DBP, and intraoperative plus postpartum intravenous fluid therapy. The length of hospital admission, number of patients requiring readmission, and number of patients requiring antihypertensive medication were also recorded for all participants. PPHTN was defined as any SBP ≥140 mm Hg or DBP ≥90 mm Hg at least 48 hours after delivery and up to 6 weeks postpartum. Blood pressures were also recorded from the outpatient office visits, when available, up to 6 weeks postpartum.

Measurement of Antepartum Circulating Angiogenic Proteins

Discarded venous EDTA blood samples collected before C-section (between 12 and 96 hours before C-section) were obtained from the hospital laboratory, and plasma was divided into aliquots and stored (between 12 and 96 hours before C-section) were obtained from the hospital laboratory, and plasma was divided into aliquots and stored at −70°C. Blood samples were missing in 7 subjects. A single operator performed quantitative sandwich ELISA for both sFlt1 and PIgF biomarkers on these discarded plasma samples from the remaining subjects (n=981) in duplicate with commercially available ELISA kits (R&D Systems, Inc, Minneapolis, MN), as described elsewhere. The interassay coefficients for sFlt1 and PIgF were 7% and 11%, respectively. The operator was blinded to clinical information. The clinicians treating the patients did not have any knowledge of the biomarker levels because the assays were done in 1 batch after the outcomes had occurred.

Patient Cohort Classification

All subjects in our study were first classified into 2 groups: normotensive pregnancy (NL: SBP <140 mm Hg and DBP <90 mm Hg before delivery; n=774 patients) and hypertensive pregnancy (HTN: SBP ≥140 mm Hg or DBP ≥90 mm Hg once before delivery; n=214 patients). These 2 groups were then further categorized as either remaining/normotensive (as defined above) or developing PPHTN (SBP ≥140 mm Hg or DBP ≥90 mm Hg) ≥48 hours after C-section. Therefore, the resultant 4 subgroups into which all subjects were categorized were NL/NL, NL/PPHTN, HTN/NL, and HTN/PPHTN.

Statistical Analysis

Antepartum, delivery, and postpartum characteristics of normotensive and hypertensive patients are presented overall and by PPHTN status as mean±SD, medians (25th–75th percentiles), or numbers and percentages. Characteristics were compared between postpartum groups with independent-samples t tests or χ² tests, as appropriate. Angiogenic factors were natural log transformed to meet the assumptions of parametric testing. Pearson correlation coefficients were used to determine the associations between natural log–transformed antepartum angiogenic factors and highest recorded antepartum and postpartum SBPs and DBPs. Separate univariate and multivariable logistic regression models were used to predict the risk of PPHTN by the overall tertile of each angiogenic factor among normotensive and hypertensive patients. Adjustment was made for variables significant in univariate models and for clinically known confounders: gestational age, body mass index, nulliparous, race, history of chronic hypertension, and history of diabetes mellitus. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to summarize the results of logistic regression models. The average days of hospitalization were compared between the normotensive and hypertensive groups with independent-samples t tests (natural log–transformed average days of hospitalization) and χ² tests. Statistical analyses were conducted with the use of SAS software version 9.4 (SAS Institute). Two-tailed values of P<0.05 were considered to indicate statistical significance.

Results

Patient Characteristics Associated With PPHTN

Among 774 normotensive pregnancies, 9.9% of these women (n=77) went on to develop de novo PPHTN (Table 1). Black
women (20.8% versus 7.0%), women with a higher body mass index at delivery (mean±SD, 34.1±7.3 versus 30.0±5.2 kg/m²), and women with a history of diabetes mellitus (13.0% versus 3.9%) demonstrated increased risk of developing de novo PPHTN compared with normotensive women who remained normotensive (all $P<0.001$). The highest recorded antepartum SBPs and DBPs, although still in the normotensive range, were significantly higher in those women developing de novo PPHTN (SBP, 127±8 versus 119±11 mm Hg; DBP, 78±7 versus 74±8 mm Hg; all $P<0.001$; Table 1).

Among 214 hypertensive pregnancies of any cause, 50.0% (n=107) remained hypertensive in the postpartum period. Similar to patients with de novo PPHTN, patients with persistent hypertension had a higher body mass index at delivery (mean±SD, 35.1±7.3 versus 32.3±5.3 kg/m²), history of hypertension (29.9% versus 3.7%), and history of diabetes mellitus (21.5% versus 5.6%) compared with women who were normotensive postpartum (all $P<0.01$). The highest recorded antepartum SBPs and DBPs were significantly higher in those women developing persistent PPHTN (SBP, 155±15 versus 141±9 mm Hg; DBP, 94±9 versus 89±7 mm Hg; all $P<0.001$) than among initially hypertensive women who became normotensive in the postpartum period (Table 2).

### Table 1. Clinical and Laboratory Characteristics of the Initially Normotensive Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All NL (n=774)</th>
<th>NL/NL (n=697)</th>
<th>NL/PPHTN (n=77)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All before delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>39±2</td>
<td>39±2</td>
<td>39±3</td>
<td>0.70</td>
</tr>
<tr>
<td>Age, y</td>
<td>33±5</td>
<td>33±5</td>
<td>32±6</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.4±5.6</td>
<td>30.0±5.2</td>
<td>34.1±7.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Nulliparous, n (%)</td>
<td>337 (43.5)</td>
<td>303 (43.5)</td>
<td>34 (44.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>14 (1.8)</td>
<td>12 (1.7)</td>
<td>2 (2.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>White</td>
<td>426 (55.0)</td>
<td>383 (55.0)</td>
<td>43 (55.8)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>65 (8.4)</td>
<td>49 (7.0)</td>
<td>16 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>119 (15.4)</td>
<td>113 (16.2)</td>
<td>6 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>164 (21.2)</td>
<td>152 (21.8)</td>
<td>12 (15.6)</td>
<td></td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>13 (1.7)</td>
<td>11 (1.6)</td>
<td>2 (2.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>37 (4.8)</td>
<td>27 (3.9)</td>
<td>10 (13.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>IVF this gestation, n (%)</td>
<td>36 (4.7)</td>
<td>31 (4.5)</td>
<td>5 (6.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Antepartum characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest SBP, mm Hg</td>
<td>120±11</td>
<td>119±11</td>
<td>127±8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Highest DBP, mm Hg</td>
<td>74±8</td>
<td>74±8</td>
<td>78±7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ALT, U/L†</td>
<td>18.9±15.1</td>
<td>21.2±18.3</td>
<td>15.0±5.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Creatinine, mg/dL†</td>
<td>0.6±0.1</td>
<td>0.6±0.1</td>
<td>0.6±0.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Uric acid, mg/dL†</td>
<td>4.6±0.9</td>
<td>4.8±0.9</td>
<td>4.5±0.8</td>
<td>0.31</td>
</tr>
<tr>
<td>Platelet count, 1000/μL</td>
<td>218±57</td>
<td>218±56</td>
<td>224±64</td>
<td>0.33</td>
</tr>
<tr>
<td>sFlt1, pg/mL‡</td>
<td>7895 (5117–12619)</td>
<td>7721 (5088–12199)</td>
<td>10 189 (5655–16650)</td>
<td>0.004*</td>
</tr>
<tr>
<td>PI GF pg/mL‡</td>
<td>243 (159–399)</td>
<td>249 (162–409)</td>
<td>214 (139–295)</td>
<td>0.06</td>
</tr>
<tr>
<td>sFlt1/PI GF ratio‡</td>
<td>34.2 (15.0–68.0)</td>
<td>33.1 (14.1–65.9)</td>
<td>52.1 (22.0–84.6)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Delivery characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3355±659</td>
<td>3348±642</td>
<td>3416±703</td>
<td>0.48</td>
</tr>
<tr>
<td>Postpartum characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated blood loss, mL</td>
<td>787±215</td>
<td>787±217</td>
<td>788±188</td>
<td>0.99</td>
</tr>
<tr>
<td>Total IV fluids§</td>
<td>2027±674</td>
<td>2036±681</td>
<td>1942±610</td>
<td>0.25</td>
</tr>
</tbody>
</table>

The NL/NL group had SBP <140 mm Hg and DBP <90 mm Hg before delivery and SBP <140 mm Hg and DBP <90 mm Hg at 48 hours to 6 weeks postpartum after cesarean section; the NL/PPHTN group had SBP <140 mm Hg and DBP <90 mm Hg before delivery and SBP ≥140 mm Hg or DBP ≥90 mm Hg at 48 hours to 6 weeks postpartum after cesarean section. Values are mean±SD, median (25th–75th percentiles), or n (%) as appropriate. ALT indicates alanine transaminase; DBP, diastolic blood pressure; IV, intravenous; IVF, in vitro fertilization; NL, normal; PI GF, placenta growth factor; PPHTN, postpartum hypertension; SBP, systolic blood pressure; and sFlt1, soluble fms-like tyrosine kinase 1.

*Significant at $P<0.05$.
†ALT=35 subjects, creatinine=40 subjects, and uric acid=28 subjects.
‡N=769 subjects for sFlt1, PI GF, and sFlt1/PI GF assays.
§Intraoperative and postpartum day 1.
There was no difference in intraoperative and postoperative intravenous fluid volumes administered between women with PPHTN and those without. More than 90% of all patients received a nonsteroidal medication, and there was no difference in doses between these 2 groups. The majority of patients (62.0%) developed PPHTN between 48 and 72 hours after delivery; another 27.2% developed the disorder on day 4; and 5.4% developed PPHTN on day 5. The remaining patients developed PPHTN after the first week. Of 184 patients with PPHTN, 39 patients had severe hypertension (defined as SBP ≥160 mm Hg or DBP ≥110 mm Hg).

Table 2. Clinical and Laboratory Characteristics of the Initially Hypertensive Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All HTN (n=214)</th>
<th>HTN/NL (n=107)</th>
<th>HTN/PPHTN (n=107)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All before delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38±3</td>
<td>39±2</td>
<td>37±3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age, y</td>
<td>33±5</td>
<td>32±5</td>
<td>34±5</td>
<td>0.03*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>33.7±6.5</td>
<td>32.3±5.3</td>
<td>35.1±7.3</td>
<td>0.002*</td>
</tr>
<tr>
<td>Nulliparous, n (%)</td>
<td>140 (65.4)</td>
<td>70 (65.4)</td>
<td>70 (65.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>3 (1.4)</td>
<td>1 (0.9)</td>
<td>2 (1.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>White</td>
<td>123 (57.5)</td>
<td>61 (57.0)</td>
<td>62 (57.9)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Black</td>
<td>29 (13.6)</td>
<td>15 (14.0)</td>
<td>14 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>13 (6.1)</td>
<td>5 (4.7)</td>
<td>8 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>49 (22.9)</td>
<td>26 (24.3)</td>
<td>23 (21.5)</td>
<td></td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>36 (16.8)</td>
<td>4 (3.7)</td>
<td>32 (29.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>29 (13.6)</td>
<td>6 (5.6)</td>
<td>23 (21.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>IVF this gestation, n (%)</td>
<td>15 (7.0)</td>
<td>8 (7.5)</td>
<td>7 (6.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Antepartum characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest SBP, mm Hg</td>
<td>148±14</td>
<td>141±9</td>
<td>155±15</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Highest DBP, mm Hg</td>
<td>91±9</td>
<td>89±7</td>
<td>94±9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ALT, U/L†</td>
<td>29.3±55.3</td>
<td>25.4±41.1</td>
<td>30.9±60.2</td>
<td>0.57</td>
</tr>
<tr>
<td>Creatinine, mg/dL†</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
<td>0.59</td>
</tr>
<tr>
<td>Uric acid, mg/dL†</td>
<td>5.3±1.1</td>
<td>5.2±1.3</td>
<td>5.3±1.1</td>
<td>0.70</td>
</tr>
<tr>
<td>Platelet count, 1000/μL</td>
<td>219±64</td>
<td>219±59</td>
<td>219±69</td>
<td>0.96</td>
</tr>
<tr>
<td>sFlt1, pg/mL†</td>
<td>12 421 (8023–18 036)</td>
<td>11 708 (7429–16 417)</td>
<td>13 067 (8660–22 816)</td>
<td>0.02*</td>
</tr>
<tr>
<td>PlGF, pg/mL†</td>
<td>174 (111–279)</td>
<td>213 (131–319)</td>
<td>148 (98–222)</td>
<td>0.002*</td>
</tr>
<tr>
<td>sFlt1/PlGF ratio‡</td>
<td>73.9 (32.2–163.3)</td>
<td>57.2 (26.0–128.8)</td>
<td>93.9 (47.3–199.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>49 (22.9)</td>
<td>7 (6.5)</td>
<td>42 (39.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>20 (9.4)</td>
<td>5 (4.7)</td>
<td>15 (14.0)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>16 (7.5)</td>
<td>3 (2.8)</td>
<td>13 (12.1)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Transient hypertension</td>
<td>129 (60.3)</td>
<td>92 (86.0)</td>
<td>37 (34.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Delivery characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3260±824</td>
<td>3393±715</td>
<td>3129±903</td>
<td>0.02*</td>
</tr>
<tr>
<td>Postpartum characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated blood loss, mL</td>
<td>842±260</td>
<td>872±305</td>
<td>811±204</td>
<td>0.08</td>
</tr>
<tr>
<td>Total IV fluids, mL§</td>
<td>1865±680</td>
<td>1920±723</td>
<td>1809±632</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The HTN/NL group was made up of patients who were initially hypertensive and normotensive postpartum. The HTN/PPHTN group was made up of patients with persistent hypertension. The diagnoses of preeclampsia, gestational hypertension, and chronic hypertension were based on International Classification of Diseases, Ninth Revision code. Subjects who had any antepartum blood pressure ≥140/90 mm Hg but without an International Classification of Diseases, Ninth Revision diagnosis had transient hypertension. Values are mean±SD, median (25th–75th percentiles), or n (%) as appropriate. ALT indicates alanine transaminase; DBP, diastolic blood pressure; HTN, hypertension; IV, intravenous; IVF, in vitro fertilization; NL, normal; PlGF, placenta growth factor; PPHTN, postpartum hypertension; SBP, systolic blood pressure; and sFlt1, soluble fms-like tyrosine kinase1.

*Significant at P<0.05.
†ALT=119 subjects, creatinine=121 subjects, and uric acid=114 subjects.
‡N=212 subjects for sFlt1, PlGF, and sFlt1/PlGF assays.
§Intraoperative and postpartum day 1.
higher antepartum sFlt1 levels compared with women who remained normotensive postpartum (median, 10 189 pg/mL [25th–75th percentiles, 5655–16650 pg/mL] versus 7721 pg/mL [25th–75th percentiles, 5088–12199 pg/mL]) and a higher sFlt1/PlGF ratio (52.1 [25th–75th percentiles, 22.0–84.6] versus 33.1 [25th–75th percentiles, 14.1–65.9]; all P<0.001; Table 3). Similar results were seen in women with persistent PPHTN compared with subjects who were normotensive postpartum among the initially hypertensive group (sFlt1/PlGF ratio, 93.9 [25th–75th percentiles, 47.3–199.3] versus 57.2 [25th–75th percentiles, 26.0–128.8]; P<0.001; Table 2).

Those in the highest tertile of antepartum circulating sFlt1 concentration (OR, 1.89; 95% CI, 1.07–3.31; P=0.03), lowest PlGF concentration (OR, 2.38; 95% CI, 1.26–4.49; P=0.008), and highest tertile of sFlt1/PlGF ratio (OR, 2.23; 95% CI, 1.24–4.04; P=0.008) were at a significantly increased risk of developing de novo PPHTN in univariate analyses, and these effects persisted after multivariable adjustment (highest sFlt1: OR, 2.29; 95% CI, 1.22–4.33; P=0.01; lowest PlGF: OR, 2.15; 95% CI, 1.10–4.20; P=0.02; and highest sFlt1/PlGF ratio: OR, 2.25; 95% CI, 1.19–4.25; P=0.01; Table 3). Similar results were seen among the initially hypertensive group. Multivariable analysis for the highest tertile of sFlt1/PlGF ratio revealed a significantly increased OR favoring the persistence of hypertension postpartum (OR, 2.61; 95% CI, 1.12–6.05; P=0.02; Table 4). Of the 988 patients, 263 patients had labor before the C-section. Excluding patients with labor before the C-section did not change the results (data not shown).

Angiogenic Factors and PPHTN

Women who developed de novo PPHTN had significantly higher antepartum sFlt1 levels compared with women who remained normotensive postpartum (median, 10 189 pg/mL [25th–75th percentiles, 5655–16650 pg/mL] versus 7721 pg/mL [25th–75th percentiles, 5088–12199 pg/mL]) and a higher sFlt1/PlGF ratio (52.1 [25th–75th percentiles, 22.0–84.6] versus 33.1 [25th–75th percentiles, 14.1–65.9]; all P<0.001; Table 1). Similar results were seen in women with persistent PPHTN compared with subjects who were normotensive postpartum among the initially hypertensive group (sFlt1/PlGF ratio, 93.9 [25th–75th percentiles, 47.3–199.3] versus 57.2 [25th–75th percentiles, 26.0–128.8]; P<0.001; Table 2).

Those in the highest tertile of antepartum circulating sFlt1 concentration (OR, 1.89; 95% CI, 1.07–3.31; P=0.03), lowest PlGF concentration (OR, 2.38; 95% CI, 1.26–4.49; P=0.008), and highest tertile of sFlt1/PlGF ratio (OR, 2.23; 95% CI, 1.24–4.04; P=0.008) were at a significantly increased risk of developing de novo PPHTN in univariate analyses, and these effects persisted after multivariable adjustment (highest sFlt1: OR, 2.29; 95% CI, 1.22–4.33; P=0.01; lowest PlGF: OR, 2.15; 95% CI, 1.10–4.20; P=0.02; and highest sFlt1/PlGF ratio: OR, 2.25; 95% CI, 1.19–4.25; P=0.01; Table 3). Similar results were seen among the initially hypertensive group. Multivariable analysis for the highest tertile of sFlt1/PlGF ratio revealed a significantly increased OR favoring the persistence of hypertension postpartum (OR, 2.61; 95% CI, 1.12–6.05; P=0.02; Table 4). Of the 988 patients, 263 patients had labor before the C-section. Excluding patients with labor before the C-section did not change the results (data not shown).

The antepartum ln (sFlt1) positively correlated with the highest postpartum SBP (r=0.26, P<0.001) and DBP (r=0.26, P<0.001); the ln (PlGF) negatively correlated with the highest postpartum SBP (r=−0.23, P<0.001) and DBP (r=−0.22, P<0.001); and the ln (sFlt1/PlGF ratio) positively correlated with highest postpartum SBP (r=0.29, P<0.001) and DBP (r=0.28, P<0.001). The predictive risk of PPHTN increased

Table 3. Risk of PPHTN With Increasing Levels of sFlt1/PlGF Ratio Among Women Who Were Initially Normotensive

<table>
<thead>
<tr>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sFlt1</td>
<td>(95% CI)</td>
<td>OR</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>21 (8.2)</td>
<td>0.89 (0.47–1.71)</td>
<td>0.73</td>
</tr>
<tr>
<td>15 (5.8)</td>
<td>2.07 (1.08–3.96)</td>
<td>0.03*</td>
</tr>
<tr>
<td>18 (7.0)</td>
<td>1.24 (0.65–2.37)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; PlGF, placenta growth factor; PPHTN, postpartum hypertension; and sFlt1, soluble fms-like tyrosine kinase-1.

*Significant at P<0.05

†Lowest tertile is highest PlGF level.

‡Adjusted for gestational age, age, body mass index, nulliparous, race, history of chronic hypertension, and history of diabetes mellitus. sFlt1, PlGF, and sFlt1/PlGF ratio were analyzed in separate models.

Table 4. Risk of PPHTN With Increasing Levels of sFlt1/PlGF Ratio Among Women Who Were Initially Hypertensive

<table>
<thead>
<tr>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sFlt1</td>
<td>(95% CI)</td>
<td>OR</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>31 (44.3)</td>
<td>1.09 (0.56–2.12)</td>
<td>0.79</td>
</tr>
<tr>
<td>26 (36.6)</td>
<td>1.73 (0.89–3.38)</td>
<td>0.11</td>
</tr>
<tr>
<td>25 (35.7)</td>
<td>2.07 (1.06–4.07)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; PlGF, placenta growth factor; PPHTN, postpartum hypertension; and sFlt1, soluble fms-like tyrosine kinase-1.

*Lowest tertile is highest PlGF level.

†Significant at P<0.05

‡Adjusted for gestational age, age, body mass index, nulliparous, race, history of chronic hypertension, and history of diabetes mellitus. sFlt1, PlGF, and sFlt1/PlGF ratio were analyzed in separate models.
common (9.9%) and that de novo PPHTN following normotensive pregnancies was

In this large, observational, clinical study at a single tertiary
care hospital, we have demonstrated that the development of
hypertension is shown for different levels of natural log–
transformed sFlt1/PlGF ratio. The sample sizes shown represent
the number of patients at risk for each 2-unit increase in ln sFlt1/PlGF ratio.

with rising levels of antepartum sFlt1/PlGF ratio among all
women (Figure).

Women developing PPHTN also experienced a significantly
longer hospitalization than those who did not (6.5±3.5 versus 5.7±3.4 days), and a higher proportion of women developing PPHTN were treated by antihypertensive medications (22.8% versus 0.5%; both P<0.001; Table 5). The sFlt1/PlGF ratio was also elevated among women who were treated with antihypertensive medications compared with those who were not (89.5 [95% CI, 37.5–165.6] versus 38.5 [95% CI, 17.1–80.4]; P<0.001; Table 6).

Discussion

In this large, observational, clinical study at a single tertiary
care hospital, we have demonstrated that the development of
de novo PPHTN following normotensive pregnancies was common (9.9%) and that 50% of women with hypertensive pregnancies demonstrated persistence of hypertension in the postpartum period. The clinical risk factors for the eventual appearance of de novo PPHTN strongly resembled those for preeclampsia. Moreover, the antepartum angiogenic factor levels central to the pathogenesis of preeclampsia—the antiangiogenic sFlt1 and the proangiogenic PlGF—followed the same pattern (higher sFlt1, lower PlGF, and higher sFlt1/PlGF ratio) and independently predicted the development of de novo and persistent PPHTN. Among all affected patients in our study, the highest tertile of the sFlt1/PlGF ratio increased the odds of developing PPHTN (both de novo and persistent) in univariate and multivariate analyses. Finally, women developing PPHTN had longer hospital stays than those who were normotensive after delivery and required more antihypertensive medications.

Limited data describing the overall incidence and risk factors for PPHTN exist in the literature.7,18,19 Most studies have been retrospective,20 have not focused on PPHTN per se,5,21 or have had a small cohort.22 To the best of our knowledge, the present work represents one of the largest clinical studies designed to specifically study PPHTN in the literature. Our finding that the development of PPHTN was common, with an incidence of nearly 18% in our cohort, was quite notable. Considering the associated maternal morbidity (and potential mortality) of unrecognized (and therefore untreated) PPHTN, this higher-than-anticipated frequency suggests that the initial postpartum medical visit may need to occur sooner than is typical, particularly for those women with risk factors. From our data, these high-risk features appear to be identical to many of those of preeclampsia: elevated body mass index, history of diabetes mellitus, and antepartum blood pressure elevation. Taken together with prior observations, our data suggest that de novo or persistent hypertension can occur even after the placenta has been delivered. Therefore, healthcare providers should alert women to and continue to be vigilant for the signs and symptoms of this disorder and to manage them promptly to avoid serious complications such as pulmonary edema or eclampsia in the postpartum period.

Indeed, evaluation of antepartum circulating angiogenic factors revealed a pattern identical to that observed in preeclampsia in these women. These data therefore suggest that women who develop de novo PPHTN may actually represent a group of women with subclinical preeclampsia that manifests as hypertension postpartum. Similarly, patients with persistent PPHTN had higher antepartum sFlt1/PlGF ratios than those who were normotensive in the postpartum period, suggesting that persistent PPHTN may represent a subgroup of patients who either may have unresolved preeclampsia resulting from delayed clearance of antiangiogenic factor or may have a severe form of preeclampsia. Our findings also extend the biology of these factors, sFlt1 and PlGF, beyond

Table 5. Length of Hospitalization and Number Treated With Antihypertensive Medication Across All Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PPNL (n=804)</th>
<th>PPHTN (n=184)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days admitted (mean±SD)</td>
<td>5.7±3.4</td>
<td>6.5±3.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Patients on antihypertensive medication, n (%)</td>
<td>4 (0.5)</td>
<td>42 (22.8)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

PPHTN indicates postpartum hypertension (normal [NL]/PPHTN+hypertensive [HTN]/PPHTN); and PPNL, normal postpartum (NL/NL+HTN/NL).

*Significant at P<0.05.

Table 6. Angiogenic Factors by Hypertensive Medication Use

<table>
<thead>
<tr>
<th>No HTN Medications*</th>
<th>HTN Medications†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN Medications†</td>
<td>No HTN Medications*</td>
</tr>
<tr>
<td>(n=942)</td>
<td>(n=46)</td>
</tr>
<tr>
<td>sFlt1, pg/mL</td>
<td>sFlt1, pg/mL</td>
</tr>
<tr>
<td>8627 (5474–13384)</td>
<td>12657 (7973–18484)</td>
</tr>
<tr>
<td>PlGF, pg/mL</td>
<td>PlGF, pg/mL</td>
</tr>
<tr>
<td>233 (149–381)</td>
<td>146 (89–297)</td>
</tr>
<tr>
<td>sFlt1/PlGF ratio</td>
<td>sFlt1/PlGF ratio</td>
</tr>
<tr>
<td>38.5 (17.1–80.4)</td>
<td>89.5 (37.5–165.6)</td>
</tr>
</tbody>
</table>

Data presented as median (25th–75th percentiles). HTN indicates hypertension; PlGF, placenta growth factor; and sFlt1, soluble fms-like tyrosine kinase-1.

*N=936 subjects for sFlt1, PlGF and sFlt1/PlGF assays.
†N=45 subjects for sFlt1, PlGF and sFlt1/PlGF assays.
‡Significant at P<0.05.
preeclampsia and into another hypertensive disorder of pregnancy. Antepartum measurement of these angiogenic factors, in combination with a woman’s other clinical risk factors for PPHTN, may better enable clinicians in the future to determine which patients require closer surveillance after delivery and closer follow-up after hospital discharge.

Some limitations of our study require mention. First, our cohort was limited to women undergoing C-section only, which may introduce bias and limit the generalizability of our findings. However, this study design was chosen to increase the time period over which we were able to collect data on postpartum blood pressure measurements because women undergoing C-section are typically hospitalized longer than those delivering vaginally. In addition, all consecutive women with singleton pregnancies undergoing C-section were included in our study, regardless of the indication for C-section, to minimize this potential bias. Furthermore, we would have preferred to have access to longitudinal blood pressure measurements beyond 1 week after delivery in all women to determine the duration of PPHTN among the affected women in our cohort. However, ambulatory blood pressure monitoring is not routinely used to monitor for postpartum preeclampsia; hence, these data were not available. Furthermore, data were not available for all patients at the 6 weeks’ follow-up in the outpatient clinic because only a fraction of our cohort delivering at our center had their postpartum care there. Another limitation of our study is that not all subjects had blood drawn routinely for preeclampsia laboratory assessment during the antepartum period. This may have led to a lack of statistical significance for some of the routine clinical laboratory tests such as uric acid or serum creatinine. Finally, we did not find significant overall morbidity in our study other than a modest increase in the duration of hospitalization. Future studies should determine whether the antepartum angiogenic profile among high-risk patients correlates with postpartum morbidity such as postpartum eclampsia or postpartum HELLP (hemolysis-elevated liver enzymes-low platelets counts) syndrome. It would also be important to evaluate whether women with PPHTN are at risk for the development of cardiovascular disease in the long term.

Conclusions

We prospectively identified the major clinical risk factors for the development of PPHTN and for the first time implicated antepartum plasma levels of the angiogenic factors sFlt1 and PlGF in the pathogenesis of this disorder. Moreover, our description of the striking clinical similarities between the factors predicting the development of de novo PPHTN and those predicting preeclampsia, coupled with the similarity of the angiogenic profile that precedes de novo PPHTN and accompanies preeclampsia, suggests that the development of de novo PPHTN may in fact represent subclinical preeclampsia.

Sources of Funding

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Disclosures

Drs Thadhani and Karumanchi are coinventors on patents related to preeclampsia biomarkers that are held at Massachusetts General Hospital and Beth Israel Deaconess Medical Center. They have financial interest in Aggamin LLC. Drs Thadhani, Karumanchi, and Rana report serving as consultants to Roche Diagnostics. Dr Karumanchi reports serving as a consultant to Siemens Diagnostics and has received research funding from Thermofisher. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Postpartum hypertension occurring ≥48 hours after delivery is a relatively common complication that is associated with significant morbidity to the mother. However, there are limited data describing the epidemiology and pathogenesis of this disorder. In this single-center clinical study of 988 women who underwent delivery by cesarean section, we demonstrate that postpartum hypertension is a relatively common complication (≈18%). Women with postpartum hypertension use more healthcare resources, as evidenced by prolonged hospitalization and greater use of antihypertensive drugs. We further demonstrate that women with postpartum hypertension have the same clinical risk factors and antepartum circulating plasma angiogenic profile as women with preeclampsia. We conclude that women with postpartum hypertension may represent a group of women with subclinical preeclampsia or unresolved preeclampsia. Future efforts should be directed at early identification of these patients and evaluation of interventions to decrease morbidity associated with this condition.
Epidemiology and Mechanisms of De Novo and Persistent Hypertension in the Postpartum Period

Arvind Goel, Manish R. Maski, Surichhya Bajracharya, Julia B. Wenger, Dongsheng Zhang, Saira Salahuddin, Sajid S. Shahul, Ravi Thadhani, Ellen W. Seely, S. Ananth Karumanchi and Sarosh Rana

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