Hypertensive disorders complicate ≈2% to 10% of all pregnancies. Among these, preeclampsia remains one of the largest single causes of maternal and fetal mortality and morbidity, whereas uncomplicated gestational hypertension carries a far better prognosis. Clinical prediction of preeclampsia may facilitate initiation of timely management to avert mortality and morbidity in the mother and infant. Raised serum uric acid (UA) is one of the characteristic findings in preeclampsia. In clinical practice, serum UA determination is considered to be a part of the workup in women with preeclampsia to monitor disease severity and aid management of these women. The association between raised serum UA and preeclamptic pregnancies was first reported almost a century ago. Reduced UA clearance secondary to reduced glomerular filtration rate, increased reabsorption, and decreased secretion may be at the origin of elevated serum levels in women with preeclampsia. Several studies have reported a positive correlation between elevated maternal serum UA and adverse maternal and fetal outcomes. A number of studies have evaluated several tests and parameters, including UA, during the first or second trimester of pregnancy, as potential predictors of preeclampsia, with mixed results, and generally with unsatisfactory sensitivity and/or specificity. In this study, we have chosen to restrict our analysis to pregnant women referred to our unit for suspected hypertension to evaluate the prognostic value of serum UA for the subsequent development of preeclampsia and for giving birth to a small-for-gestational-age (SGA) infant, thus allowing us to identify the subgroup of hypertensive women at greater risk, necessitating of closer monitoring and surveillance.

Patients and Methods

Between July 2008 and July 2010, after obtaining their consent, we screened 206 nulliparous women submitted to our unit for suspected hypertension during pregnancy. Inclusion criteria were age >18 years, singleton pregnancy beyond the 20th week, blood pressure (BP) >140 mm Hg systolic or 90 mm Hg diastolic, and 24-hour proteinuria <300 mg. Known heart disease, nephropathy, or hypertension preceding pregnancy were reasons for exclusion from the study. None of the subjects were treated with antihypertensive drugs on entry. As the patients entered the study, BP was obtained on 2 separate occasions, ≥6 hours apart, in a quiet environment with the...
subject seated. A physician on the hospital staff measured BP with a standard mercury sphygmomanometer. In our institution, all of the mercury sphygmomanometers are calibrated every 3 months against a standard mercury sphygmomanometer. In our institution, all of the BP recordings from the first hour of monitoring were removed from analysis because they might be influenced by an alarm reaction. All of the read-ings of a pulse pressure <20 mm Hg, a diastolic BP >140 mm Hg or <90 mm Hg, or a systolic BP >250 mm Hg or <60 mm Hg were automatically rejected. The quality of 24-hour BP monitoring was judged satisfactory when ≥70% of the readings passed the editing criteria and ≥1 recording per hour was obtained. Daytime was defined as 7:00 AM to 11:00 PM. All of the women were followed up at our hospital until the end of pregnancy and regularly ≤1 month after delivery, unless their clinical conditions dictated otherwise. The outcome of pregnancy was recorded, and clinical parameters regarding the newborn (weight, Apgar score, and duration of hospital stay) were also recorded. Preeclampsia was defined as gestational hypertension and proteinuria >300 mg in a timed 24-hour sample. Transient gestational hypertension was defined as the presence of normal office BP <140 mm Hg systolic and <90 mm Hg diastolic) 4 weeks after delivery in untreated women who had hypertension without pre-eclampsia during the third trimester of pregnancy. For the purpose of

Table 1. Demographic, Laboratory, Blood Pressure, and Perinatal Parameters of the Subjects Studied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=163)</th>
<th>Gestational Hypertension (n=90)</th>
<th>Preeclampsia (n=73)</th>
<th>P Preeclampsia vs Gestational Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30.4±4.1</td>
<td>31.7±5.2</td>
<td>28.8±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestation wk at inclusion</td>
<td>34.4±3.0</td>
<td>34.5±2.9</td>
<td>34.2±2.9</td>
<td>0.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3±2.9</td>
<td>24.6±3.0</td>
<td>24.0±2.7</td>
<td>0.22</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>114±13</td>
<td>112±13</td>
<td>118±11</td>
<td>0.002</td>
</tr>
<tr>
<td>Platelets, ×1000/mm³</td>
<td>195±55</td>
<td>216±51</td>
<td>170±48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>4.4±0.7</td>
<td>4.4±0.7</td>
<td>4.3±0.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>69.9±15.7</td>
<td>63.3±7.8</td>
<td>78.1±18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UA, μmol/L</td>
<td>297±101</td>
<td>232±48</td>
<td>393±77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First-trimester UA, μmol/L</td>
<td>196±18</td>
<td>202±19</td>
<td>190±23</td>
<td>0.18</td>
</tr>
<tr>
<td>Proteinuria, mg/24 h</td>
<td>104±76</td>
<td>88±46</td>
<td>122±84</td>
<td>0.001</td>
</tr>
<tr>
<td>Perinatal parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestation wk at delivery</td>
<td>38.7±2.3</td>
<td>39.6±0.9</td>
<td>37.6±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neonatal birth weight, g</td>
<td>3060±740</td>
<td>3397±447</td>
<td>2645±819</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGA, %</td>
<td>27.6</td>
<td>9.0</td>
<td>47.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placental weight, g</td>
<td>613±139</td>
<td>668±90</td>
<td>542±158</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apgar score, 1 min (% &lt;10)</td>
<td>28.8</td>
<td>23.3</td>
<td>35.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Cesarean section, %</td>
<td>39.0</td>
<td>32.0</td>
<td>48.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Length of hospital stay, newborn, d</td>
<td>10.7±13.8</td>
<td>5.7±3.1</td>
<td>16.6±14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of hospital stay, mother, d</td>
<td>6.6±3.3</td>
<td>5.4±1.9</td>
<td>8.8±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic systolic BP, mm Hg</td>
<td>146±10.4</td>
<td>143.9±8.4</td>
<td>149.0±11.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinic diastolic BP, mm Hg</td>
<td>94.6±6.7</td>
<td>91.5±6.6</td>
<td>96.1±6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM, systolic BP, 24-h average, mm Hg</td>
<td>123.8±13.7</td>
<td>118.2±12.3</td>
<td>130.7±12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM, systolic BP, daytime average, mm Hg</td>
<td>126.9±14.1</td>
<td>122.2±13.5</td>
<td>132.7±12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM, systolic BP, nighttime average, mm Hg</td>
<td>117.9±15.4</td>
<td>110.8±12.9</td>
<td>126.6±13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM, diastolic BP, 24-h average, mm Hg</td>
<td>73.8±9.8</td>
<td>68.7±7.6</td>
<td>80.0±8.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM, diastolic BP, daytime average, mm Hg</td>
<td>76.3±10.1</td>
<td>71.3±8.2</td>
<td>82.4±8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM, diastolic BP, nighttime average, mm Hg</td>
<td>69.1±10.7</td>
<td>63.7±8.4</td>
<td>75.7±10.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; UA, uric acid; BP, blood pressure; ABPM, ambulatory blood pressure measurement; SGA, small for gestational age.
the present study, SGA infants were defined as those weighing less
than the 10th centile, based on nationwide derived centile charts for
singleton births.17

All of the results are expressed as mean±SD, unless otherwise
indicated. Comparisons between groups were performed using the
unpaired Student t test for continuous variables and the Fisher exact
test for proportions. Strength of association of UA with the outcomes
(development of preeclampsia and SGA) was assessed by binary
logistic regression, unadjusted first, and after adjustment for age,
gestation week, serum creatinine, hemoglobin and platelet levels,
and both office and ambulatory BPs; association of serum UA and
other variables with birth weight centiles was evaluated by a multiple
linear regression model. Predictive accuracy of laboratory and BP
parameters was assessed by calculating the areas under the receiver
operating characteristic curves, which were compared according to
the method of Hanley and McNeil18; optimal cutoff values were
chosen as the point on the receiver operating characteristic curve,
closest to the top left corner. P values ≤0.05 were considered as
significant. All of the calculations were performed using the SPSS
15.0 (SPSS Inc, Chicago, IL) and Medcalc 9.1 (Mariakerke,
Belgium) software.

The study was approved by the hospital ethics committee. Because
the study parameters were noninvasive and obtained as part of a
routine clinical management, the committee did not require signed
informed consent; however, verbal informed consent was obtained in
all of the cases.

Results
Overall, 163 women completed the study; among those who
did not, 20 were excluded because they did not meet the BP
criteria on entry, 3 because of proteinuria >300 mg/24 hours,
7 because of incomplete clinical data, and 11 because of
insufficient quality of the ambulatory BP monitoring record-
ings, and 2 withdrew their consent.

Seventy-three women (44.7%) developed preeclampsia,
and 43 SGA infants (26.4%) were born. One stillbirth
occurred. The average interval between time of study entry
and preeclampsia diagnosis was 14.7±5.1 days.

Demographic, laboratory, perinatal, and BP parameters are
shown in Table 1. Women who developed preeclampsia
tended to be younger and have higher levels of UA, hemog-
lbin, and creatinine; lower levels of platelets; a higher
incidence of cesarean section and SGA infants; and both
higher office and monitored BP.

Table 2 shows the results of logistic regression analysis:
the unadjusted odds ratio for UA associated with the de-
velopment of preeclampsia was 9.1 (95% CI: 4.8 to 17.4;
P<0.001), and after adjustment for age, gestation week,
serum creatinine and platelet levels, office systolic and diastolic
BPs, and 24-hour average systolic and diastolic BPs, it was 7.1 (95% CI: 3.2 to 15.7; P<0.001).

When the association between maternal serum UA and the
case of giving birth to an SGA infant was considered, the
unadjusted odds ratio was lower (1.6; 95% CI: 1.1 to 2.4;
P=0.001), and after adjusting for confounders it was 1.6
(95% CI: 1.1 to 2.3; P=0.02). In this regression model,
first-trimester UA was not significantly associated with either
preeclampsia or SGA (Table 2). Table 3 shows the results of
multiple linear regression, with birth weight centile as the
dependent variable: again, serum UA and monitored diastolic
BP 24-hour average were the only variables significantly
associated with birth weight centile. Hyperuricemic (UA
>309 μmol/L; n=9) women who did not develop preeclamps-
ia had a higher incidence of SGA compared with normouri-
cemic women (22.2% versus 4.9%; P=0.05).

Receiver operating characteristic analysis (Table 4) showed
that serum UA was an accurate predictor of pre-
eclampsia in this population (areas under the receiver oper-
ating characteristic curve: 0.955; sensitivity: 87.7%; speci-
ficity: 93.3%; positive predictive value: 91.4%; negative
predictive value: 9.6%, for a cutoff of 309 μmol/L [5.2
mg/dL]), as well as serum UA increase from first trimester
(areas under the receiver operating characteristic curve:
0.961; sensitivity: 90.4%; specificity: 97.8%; positive predic-
tive value: 97.1%; negative predictive value: 7.4%, for a
cutoff of 113 μmol/L [1.9 mg/dL]); a combination of the
above criteria (either UA level >309 μmol/L or an increase
>113 μmol/L) yielded a sensitivity of 93.6% and a specifi-
city of 91.8% (positive predictive value: 90.2%; negative
predictive value: 5.2%).
Table 3. Results of Multiple Linear Regression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B Coefficient</th>
<th>Standardized β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA, µmol/L</td>
<td>-0.428</td>
<td>-0.28</td>
<td>0.01</td>
</tr>
<tr>
<td>First-trimester UA, µmol/L</td>
<td>1.46</td>
<td>0.02</td>
<td>0.80</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>-2.05</td>
<td>-0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>Platelets, ×1000/mm³²</td>
<td>0.02</td>
<td>0.04</td>
<td>0.61</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>9.80</td>
<td>0.07</td>
<td>0.52</td>
</tr>
<tr>
<td>Ambulatory 24-h average,</td>
<td>-0.04</td>
<td>-0.02</td>
<td>0.84</td>
</tr>
<tr>
<td>systolic BP, mm Hg</td>
<td>-0.69</td>
<td>-0.26</td>
<td>0.01</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>0.21</td>
<td>0.08</td>
<td>0.33</td>
</tr>
<tr>
<td>Gestation wk</td>
<td>0.95</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>-0.16</td>
<td>-0.04</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Dependent variables was birth weight centile; independent variables were as follows: age, gestation wk, serum creatinine, UA (current and first-trimester levels), hemoglobin and platelet levels, office and ambulatory systolic and diastolic BPs. UA indicates uric acid; BP, blood pressure.

First-trimester UA was a poor predictor of preeclampsia, and it showed a sensitivity of ≈80% but unacceptably poor specificity for SGA prediction (Table 4). Regarding BP parameters (Table 4), monitored BP performed better than office BP and diastolic better than systolic BP for the prediction of both preeclampsia and SGA, although not as well as UA.

Discussion

In this sample of women with gestational hypertension, we have identified UA as a reliable predictor of preeclampsia. Although the literature reporting predictive indicators for preeclampsia is fairly extensive, evidence on the accuracy of various tests to predict preeclampsia in women with gestational hypertension is sparse and based mostly on retrospective analyses, rather than on cohort studies, such as the one we are reporting. Recently, several studies, mostly retrospective, have shown an association between first-trimester UA and the later development of preeclampsia and/or SGA. In our sample of patients (which included only women with suspected gestational hypertension), first-trimester UA was not associated so strongly with adverse outcomes; actually, although a fairly sensitive marker for SGA (86.0% sensitivity), it lacked specificity. Conversely, when measured at the moment of initial hospital admission, at first diagnosis of pregnancy-induced hypertension, UA (and even better, its increase from first trimester) carries a much higher prognostic value, with a strong correlation to adverse maternal outcomes, as reported in 2 recent retrospective studies. However, retrospective, case-control studies are known to provide more “optimistic” results regarding the predictive capability of a model, with respect to cohort studies, because of the fact that, in case-control studies, controls are generally on the healthy side of the disease spectrum, whereas cases generally display the most severe presentation of a given disease. In this respect, we believe our prospective study lends stronger support for a role of UA as a predictor of preeclampsia and/or SGA.

The debate is still open whether UA is a simple marker of disease or has a causal role in the development of preeclampsia and/or retarded fetal growth. Although the cause of hyperuricemia in preeclampsia has not definitively been elucidated, current evidence suggests that decreased renal clearance is probably the most important mechanism. However, the increase in UA levels is too large to be attributed solely to the reduction of glomerular filtration rate; thus, there must also be decreased secretion or increased reabsorption. This phenomenon appears to be analogous to the decrease in urate clearance produced by the infusion of vasoconstrictors, such as norepinephrine, and to the increase of blood UA clearance, there may occur increased placental production of UA secondary to placental ischemia and increased tropho-
blast shedding, leading to further purine availability for breakdown. Fetuses exposed to hypoxia (eg, secondary to decreased placental perfusion) have been shown to have increased serum levels of purine metabolites.\textsuperscript{24} In preeclampsia, therefore, it is conceivable that these metabolites can cross into the maternal circulation to be degraded by maternal xanthine oxidase. These latter mechanisms might explain the relationship between raised UA levels and fetal growth retardation. An active role for UA in the development of preeclampsia has been proposed: studies in animals have suggested that UA may play a more active part in the development of hypertension in preeclampsia and perhaps later in life.\textsuperscript{25,26} UA has been shown to induce endothelial dysfunction in humans\textsuperscript{27,28} and, recently, to be able to induce human trophoblast production of interleukin 1\(\beta\) by activating the Nod-like receptor Nalp 3, thus stimulating the expression of inflammasome components.\textsuperscript{29}

Finally, regarding BP parameters, the findings of our study show that ambulatory BP monitoring derived measures are better predictors of preeclampsia and (to a lesser extent) SGA, with respect to office BP, probably because of the high prevalence of white-coat hypertension in the pregnant population\textsuperscript{30}; however, only 24-hour average diastolic BP was significantly associated with SGA and birth weight centile and showed a borderline significant association with preeclampsia.

**Perspectives**

In conclusion, we believe the findings of our study show that, in women with suspected hypertension in pregnancy, serum UA >309 \(\mu\)mol/L can accurately predict the later development of preeclampsia and, more so, an increment >113 \(\mu\)mol/L from first-trimester levels. We provide threshold values that might prove useful in clinical practice, although, of course, further studies are necessary.

**Disclosures**

None.

**References**

Prognostic Significance of Serum Uric Acid in Women With Gestational Hypertension
Gianni Bellomo, Sandro Venanzi, Paolo Saronio, Claudio Verdura and Pier Luca Narducci

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