Altered Excretion of Prostaglandin and Thromboxane Metabolites in Pregnancy-Induced Hypertension

PIETRO MINUZ, GRAZIA COVI, FRANCESCA PALUANI, MAURIZIO DEGAN, CLARA LECHI, MARISA CORSATO, AND ALESSANDRO LECHI

SUMMARY The renal and systemic metabolites (the latter as 2,3-dinor derivatives) of prostacyclin and thromboxane A₂ were measured, along with renal prostaglandin E₂ and kallikrein, in the urine of 15 patients with pregnancy-induced hypertension, 15 normotensive pregnant women matched for both age and gestational age, and 15 normotensive nonpregnant control women. Urinary excretion of all prostaglandin and thromboxane metabolites studied proved significantly higher in normotensive pregnant women than in controls. Prostaglandin E₂, 6-keto-prostaglandin F₁α, and 2,3-dinor-6-keto-prostaglandin F₁α were significantly lower in pregnancy-induced hypertensive women than in normotensive pregnant women, whereas thromboxane B₂ and 2,3-dinor-thromboxane B₂ showed no significant differences in the two groups. A significant negative correlation (r = −0.636, p < 0.01) was found between urinary 2,3-dinor-6-keto-prostaglandin F₁α and mean blood pressure in the two groups of pregnant women taken as a whole. These data indicate that, in pregnancy-induced hypertension, there is an imbalance between vasodilator and vasoconstrictor factors, not only in the kidneys, but also at the systemic vascular level. This imbalance, which may in itself produce vasoconstriction, may also potentiate the hypertensive effect of catecholamines and angiotensin II. (Hypertension 11: 550-556, 1988)

KEY WORDS • pregnancy-induced hypertension • prostaglandins • prostacyclin • thromboxane A₂ • kallikrein

PREGNANCY-INDUCED hypertension (PIH) is defined as systemic arterial hypertension (diastolic blood pressure > 85 mm Hg or mean blood pressure > 95 mm Hg) appearing in the third trimester of pregnancy, often associated with edema and proteinuria.¹ A number of hypotheses have been advanced regarding the pathogenesis of PIH, but the ultimate mechanism responsible for blood pressure elevation is still unknown. PIH has been attributed to one or more of the following factors: impaired renal function,² inappropriate activation of the renin-angiotensin-aldosterone system,³ and decreased production of progestational compounds.⁴ A certain amount of emphasis has been placed in recent years on the role of vasoactive factors such as kinins and prostaglandins.⁵⁻⁸

By acting as vasodilators and natriuretic factors, prostaglandin E₂ (PGE₂) and kinins might in some way be involved in the regulation of plasma volume.⁹,¹⁰ Vasodilator prostaglandins, particularly prostacyclin (PGI₂), appear to play an important role in the control of vascular reactivity, platelet aggregability, and renal and uteroplacental blood flow during normal pregnancy, whereas thromboxane A₂ (TXA₂) is known to have the opposite effect.¹¹ An imbalance between these two compounds might account for some of the phenomena characterizing PIH. On the basis of these observations, then, the renal prostaglandin system appears to be somehow involved in the sequence of events leading to the full clinical development of PIH.

Since renal involvement in PIH is not enough in itself to account for systemic hypertension, the aim of our study was to evaluate not only the urinary excretion of PGE₂, kallikrein, and the renal metabolites of PGI₂ and TXA₂, but also the 2,3-dinor metabolites of PGI₂ and TXA₂ deriving from the systemic production
of these two compounds\textsuperscript{12} in a group of women with PIH as compared with normotensive pregnant subjects.

**Subjects and Methods**

Fifteen women with PIH and 15 age-matched normotensive pregnant control subjects were studied, all between Weeks 30 and 35 of pregnancy. The study was performed simultaneously in the two groups, the clinical characteristics of which are summarized in Table 1. None of the women studied had any history of arterial hypertension, and all had plasma creatinine values below 95 $\mu$mol/L. Patients with urinary tract infections were excluded from the study.

The women with PIH were selected on the basis of the generally accepted criteria for systemic arterial hypertension appearing after the 20th week of pregnancy (systolic blood pressure $>$ 140 mm Hg or diastolic blood pressure $>$ 90 mm Hg, or both) with or without proteinuria or edema. Blood pressure values returned to normal in all PIH subjects within 3 months of the end of pregnancy. At the time of the study, the subjects with PIH showed no clinical signs of disseminated intravascular coagulation, and laboratory test results for coagulation (platelet count, prothrombin time, and plasma fibrinogen levels) were normal. All subjects were hospitalized in a clinical ward of a university hospital and were put on a normocaloric diet without salt restriction. All parameters considered were assessed in the course of a single day.

Blood pressure in the upright position was measured after 2 minutes of active standing; the supine position was maintained for 3 hours before measurements. Blood pressure, in both the upright and left-side recumbent positions, was measured with a standard cuff and mercury sphygmomanometer using Korotkoff Phase V for the recordings. Blood samples for plasma renin activity (PRA) determinations were collected in Phase V for the recordings. Blood samples for plasma fibrinogen levels were normal. All subjects to normal in all PIH subjects within 3 months of the end of pregnancy. At the time of the study, the subjects with PIH showed no clinical signs of disseminated intravascular coagulation, and laboratory test results for coagulation (platelet count, prothrombin time, and plasma fibrinogen levels) were normal. All subjects were hospitalized in a clinical ward of a university hospital and were put on a normocaloric diet without salt restriction. All parameters considered were assessed in the course of a single day.

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**Laboratory Procedures**

PGE\textsubscript{2} and the urinary metabolites of PGF\textsubscript{2}\alpha and TXA\textsubscript{2} were determined by radioimmunoassay. We took urinary excretion of 6-keto-prostaglandin F\textsubscript{1a} (6-keto-PGF\textsubscript{1a}) and thromboxane B\textsubscript{2} (TXB\textsubscript{2}) as indices\textsuperscript{12} of renal PG\textsubscript{1} and TXA\textsubscript{2} production; the indices used for the systemic production of PG\textsubscript{1} and TXA\textsubscript{2} were urinary excretion of 2,3-dinor-6-keto-PGF\textsubscript{1a} and 2,3-dinor-TXB\textsubscript{2}, respectively.

Urine samples were purified by means of chromatographic procedures before the assays. The method has been partly described previously\textsuperscript{13}. 20-ml urine samples were centrifuged (for 10 minutes at 1000 $g$) and acidified with citric acid (pH 3.0–3.4); approximately 6000 dpm of $[^{3}H]6$-keto-PGF\textsubscript{1a} (150 Ci/mmol, Bucking- hamshire, Amersham, UK) was then added to each sample. As a first chromatographic step, the urine samples were passed through Sep-Pak C\textsubscript{18} cartridges (Waters, Milford, MA, USA, pretreated with ethanol (20 ml) and water (20 ml). All solvents used were analytical grade (ACS Carlo Erba, Milan, Italy). Cartridges were then eluted with water (20 ml), ethanol/water (15:85, 20 ml), petroleum ether (20 ml), and ethyl acetate (10 ml). This fraction, containing prostaglandin and thromboxane metabolites, was collected and immediately passed through disposable silica columns (J. T. Baker Chemical, Phillipsburg, NY, USA), previously washed with ethyl acetate/toluene (20:80; 5 ml). Columns were then rinsed with ethyl acetate/toluene (40:60; 5 ml) and ethyl acetate/toluene/methanol (40:60:20; 10 ml). This fraction, after vacuum drying and suspension in acetonitrile/water (30:70; 300 $\mu$L; high performance liquid chromatography [HPLC] grade, Carlo Erba), was subjected to the HPLC procedure. The HPLC apparatus used was a Beckman 112 solvent delivery module (Berkeley, CA, USA). A reverse-phase octadecyl-silane column was used (Hyperchrome ODS2, 15 x 4.6 cm, 5 $\mu$m; Bishoff, Leonberg, FRG). Prostaglandin and thromboxane metabolites were eluted isocratically with acetonitrile/water (30:70; acidified to pH 3 with trifluoroacetic acid). Flow rate was 1 ml/min. Good separation of PG\textsubscript{1} and TXA\textsubscript{2} metabolites was obtained.\textsuperscript{14} Two fractions were collected, the first containing both 2,3-dinor-TXB\textsubscript{2} and 2,3-dinor-6-keto-PGF\textsubscript{1a}. These fractions were extracted with ethyl acetate, vacuum dried, and suspended in 0.02 M phosphate buffer, pH 7.4. The recovery of $[^{3}H]6$-keto-PGF\textsubscript{1a} added to each sample was 28.6 ± 15% (mean ± SD) at the end of the purification procedure. Recovery rates in our laborato-
ry are approximately 45% for PGE₂ and approximately 35% for the other compounds (subjected to the HPLC procedure).

Radioimmunooassay of 6-keto-PGF₁α has been described elsewhere.¹¹ Urinary TXB₂ and PGE₂ were measured using antisera produced by the Pasteur Institute, Paris, France. We used an antisera produced in our laboratory for the assay of 2,3-dinor-6-keto-PGF₁α. This antisera has high cross-reactivity with 6-keto-PGF₁α (about 100%), but low cross-reactivity with TXA₂ metabolites (<0.02%).

[³H]6-Keto-PGF₁α (specific activity, 150 Ci/mmol; Amersham) was used as a tracer, and authentic 2,3-dinor-6-keto-PGF₁α was used as the standard in the incubating mixture. For the radioimmunooassay of 2,3-dinor-TXB₂, we used anti-TXB₂ sera produced by the Pasteur Institute, which also showed high affinity for 2,3-dinor-TXB₂. [³H]TXB₂ and authentic 2,3-dinor-TXB₂ were used in the assay. Dilution and recovery tests were performed for validation of the assay. The results were also compared with those obtained using different antisera. 2,3-Dinor-6-keto-PGF₁α and 2,3-dinor-TXB₂ assays were also validated by comparison with the results obtained with gas chromatography-mass spectrometry in the laboratory directed by Dr. G. FitzGerald, Vanderbilt University, Nashville, TN, USA. The intra-assay variability ranged from 4.9 to 9% for all the prostanoids studied, and the interassay variability ranged from 9 to 14.6%.

PRA was measured by radioimmunooassay of the angiotensin I generated.¹³ Urinary kallikrein excretion was determined by means of a slightly modified colorimetric method.¹⁴ Before the enzyme assay, the urine samples (2.5 ml) were eluted through Sephadex 625 columns with 0.01 M Tris HC₁, pH 8.5, to remove low-molecular-weight inhibitors and salts. Blood urea, creatinine, electrolytes, and uric acid were determined using a Technicon SMA II multichannel autoanalyzer (Tarrytown, NY, USA). Human placental lactogen and estriol were measured by radioimmunooassay.

Data Analysis
The data are expressed as mean values ± SEM, unless otherwise indicated. The results were analyzed using Student's t test for grouped comparisons, preceded by one-way analysis of variance. Differences with a p level less than 0.05 were regarded as significant. Correlations were calculated by means of linear regression analysis.

Results
Blood pressure values in both the upright and lateral recumbent positions were significantly different in the two groups (normotensive pregnant women and women with PIH; see Table 1). The time of delivery was earlier in women with PIH than in normotensive pregnant controls, as delivery was brought forward in six PIH women because of their preeclamptic condition. The offsprings' birth weight was consequently lower in patients with PIH, in all probability because of the shorter length of pregnancy, whereas placental weight showed no significant difference in the two groups. Of the laboratory parameters studied (Table 2), plasma uric acid and creatinine concentrations were higher, and urinary creatinine excretion lower, in the PIH group. PRA was lower in PIH subjects only in the upright position. No significant differences were observed between normotensive pregnant women and women with PIH as far as hematocrit and placental hormones (human placental lactogen, estriol) were concerned.

The excretion of all the prostanoid compounds studied was significantly higher in normotensive pregnant women than in nonpregnant control women (Table 3). Urinary kallikrein was found to be slightly, but not significantly, higher in normotensive pregnant women.

On comparing the data for the renal vasodilator compounds obtained in the two study groups (normotensive pregnant women and women with PIH), we found a markedly reduced urinary excretion of 6-keto-PGF₁α and PGE₂ in the PIH group (Figure 1). Equally, women with PIH showed a reduced excretion of PGI₂ systemic metabolites (Figure 2). On the other hand, urinary excretion of TXB₂ and 2,3-dinor-TXB₂, the metabolite of systemic TXA₂, was found to be similar in the two groups (see Figures 2 and 3).

A significant correlation (r = −0.636, p < 0.01) was found between urinary 2,3-dinor-6-keto-PGF₁α and mean blood pressure in the two groups of pregnant women taken together (Figure 4). There was also a significant correlation between supine PRA and urinary TXB₂ in the PIH group only (Figure 5). Finally, urinary kallikrein (Figure 6) was significantly reduced in women with PIH as compared with normotensive pregnant women.

Discussion
In previous studies, an increase in plasma and urinary PGE₂ and PGI₂ metabolites has been observed in normal pregnancy, and this phenomenon is thought to be related, at least hypothetically, to the cardiocirculatory changes characterizing this condition.⁷ ¹⁷ ¹⁸ Indi-

### Table 2. Biochemical Findings in Normotensive Pregnant Women and in Women with Pregnancy-Induced Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>NP (n = 15)</th>
<th>PIH (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>33.5 ± 3.0</td>
<td>34.0 ± 3.4</td>
</tr>
<tr>
<td>Serum uric acid (μmol/L)</td>
<td>232 ± 57</td>
<td>410 ± 110*</td>
</tr>
<tr>
<td>Supine PRA (ng Ang I/ml/hr)</td>
<td>4.7 ± 3.0</td>
<td>3.2 ± 1.1</td>
</tr>
<tr>
<td>Upright PRA (ng Ang I/ml/hr)</td>
<td>8.4 ± 3.4</td>
<td>5.4 ± 2.6t</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>51.3 ± 8.7</td>
<td>71.6 ± 15.6*</td>
</tr>
<tr>
<td>Urinary creatinine (mmol/24 hr)</td>
<td>11.3 ± 2.4</td>
<td>8.7 ± 1.9*</td>
</tr>
<tr>
<td>Serum estriol (nmol/L)</td>
<td>99.1 ± 39.5</td>
<td>95.6 ± 61.9</td>
</tr>
<tr>
<td>Serum HPL (mg/L)</td>
<td>8.1 ± 3.0</td>
<td>6.9 ± 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SD. NP = normotensive pregnant women; PIH = women with pregnancy-induced hypertension; Ang I = angiotensin I; HPL = human placental lactogen

* p < 0.005, t p < 0.05, compared with values in the NP group.
TABLE 3. Urinary Excretion of Prostanoid Compounds and Kallikrein in Nonpregnant Control Women, Normotensive Pregnant Women, and Women with Pregnancy-Induced Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 15)</th>
<th>NP (n = 15)</th>
<th>PIH (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE(_2) (ng/24 hr)</td>
<td>169 ± 23</td>
<td>993 ± 243*</td>
<td>255 ± 55†</td>
</tr>
<tr>
<td>6-keto-PGF(_{1α}) (ng/24 hr)</td>
<td>239 ± 26</td>
<td>1407 ± 242*</td>
<td>726 ± 135*‡</td>
</tr>
<tr>
<td>TXB(_2) (ng/24 hr)</td>
<td>57 ± 8</td>
<td>121 ± 15§</td>
<td>91 ± 18</td>
</tr>
<tr>
<td>2,3-dinor-6-kcto-PGF(_{α}) (pg/mg creatinine)</td>
<td>220 ± 29</td>
<td>831 ± 174*</td>
<td>291 ± 55†</td>
</tr>
<tr>
<td>2,3-dinor-TXB (pg/mg creatinine)</td>
<td>156 ± 38</td>
<td>462 ± 100*</td>
<td>448 ± 122</td>
</tr>
<tr>
<td>Kallikrein (μmol p-NA/24 hr)</td>
<td>7.7 ± 0.6</td>
<td>11.3 ± 2.0</td>
<td>4.6 ± 0.5§</td>
</tr>
</tbody>
</table>

Values are means ± SEM (one-way analysis of variance and Student's t test for grouped comparisons). NP = normotensive pregnant women; PIH = woman with pregnancy-induced hypertension.

*p<0.01, §p<0.05, compared with control values.
†p<0.01, ‡p<0.05, compared with the NP group values.

Rect confirmation of this hypothesis is provided by the fact that indomethacin administration restores the normal vascular reactivity of angiotensin II, which is physiologically depressed during pregnancy. Our results confirm the increased excretion of vasodilator prostaglandins during normal pregnancy already described elsewhere. In this group, the variability is very high and is related neither to urinary volume nor to urinary creatinine excretion; this variability might indicate that a very strong activation of vasodilator factors occurs in some subjects in this condition. However, not only were high levels of urinary metabolites of vasodilator prostaglandins observed, but also TXA\(_2\) metabolites were found to be increased, though to a lesser extent. This finding indicates that a general activation of the prostaglandin system takes place during pregnancy.

In normal pregnancy, both the renin-angiotensin-aldosterone and the kallikrein-kinin systems have been found to be activated, but this activation is not significantly related to increased prostaglandin production. Accordingly, in our group of normal pregnant women, we found no correlation between PRA or urinary kallikrein and prostaglandin excretion. An alternative ex-
planning may be that hormonal regulation of prostaglandins and TXA₂ by estrogens and progesterone may be involved in pregnancy. Progesterone has been shown to stimulate PGI₂ production by the aorta and myometrium in vitro, while both TXA₂ and prostaglandins have been shown to be produced in vitro by all pregnancy-associated tissues. The data available at this point, however, are discordant.

A marked alteration occurred in urinary excretion of vasodilator compounds in PIH. Renal kallikrein, PGE₁, and 6-keto-PGF₁α were significantly reduced as compared with levels in normotensive pregnancy, though urinary 6-keto-PGF₁α was still higher than in nonpregnant women. Urinary excretion of TXB₂, on the other hand, showed no significant difference in PIH and in normal pregnancy. Our results are consistent with those reported by Pedersen et al., at least as far as PGE₁ is concerned.

PGI₂ and thromboxane in the kidney exert opposite effects on plasma flow and glomerular filtrate, particularly in conditions characterized by hyperreactivity of the renin-angiotensin system, as is the case in pregnancy. The increased production of PGI₂ in this condition may contribute toward increasing renal flow, thus indicating vasodilatation. Consequently, in PIH, an imbalance in production of the two compounds with a relatively higher output of TXA₂ as compared with PGI₂ might account for the reductions observed in glomerular filtrate and diuresis.

In conditions of relative PGI₂ deficiency such as in PIH, we observed a significant correlation between PRA and urinary TXB₂. This phenomenon deserves

FIGURE 2. Urinary excretion of 2,3-dinor-6-keto-PGF₁α and 2,3-dinor-thromboxane B₂ (2,3-dinor-TXB₂) in nonpregnant normotensive control women (C), normotensive pregnant women (NP), and women with pregnancy-induced hypertension (PIH). Single (p<0.05) and double asterisks (p<0.01) indicate significant difference between groups. Bars indicate means ± SEM.

FIGURE 3. Urinary excretion of thromboxane B₂ (TXB₂) in nonpregnant normotensive control women (C), normotensive pregnant women (NP), and women with pregnancy-induced hypertension (PIH). Asterisk (p<0.01) indicates significant difference between groups. Bars indicate means ± SEM.

FIGURE 4. Correlation between 2,3-dinor-6-keto-PGF₁α urinary excretion and mean blood pressure in left-side recumbent position in normotensive pregnant women (○) and women with pregnancy-induced hypertension (●).

\[ y = 110 - 0.026x \]
\[ r = -0.636 \]
\[ p < 0.01 \]
attention in view of the relationship of reciprocal positive action existing between the renin-angiotensin system and thromboxane in the kidney.24-2627 Despite the increase in arterial blood pressure and the reduction in effective plasma volume in PIH, a reduction in PRA in PIH has been found on several occasions as compared with normal pregnancy,28-30 and the same phenomenon was also observed in our patients. This reduction may depend, in turn, on reduced renal production of PGI2, which is known to be a powerful stimulator of renin secretion.31 The phenomenon is not a constant finding, and some authors, by contrast, have reported an increase in PRA and in plasma angiotensin II levels in PIH.3 Despite this effect, the renin-angiotensin system is less active in PIH, and adrenergic activity, as assessed indirectly by plasma catecholamine assay,8,33 is not increased. All of these factors suggest that other vasoactive factors such as PGI2 and TXA2 may play an important role in modifying systemic vascular reactivity.

As already mentioned, urinary excretion of 6-keto-PGF1α and TXB2 is regarded as mainly reflecting the production of PGI2 and TXA2 in the kidney.12 The urinary dinor metabolites are regarded as representing a substantial amount of, and thus as being a reliable index for, systemic production of PGI2 and TXA2,12 the vascular endothelium being an important source of PGI2 synthesis, while TXA2 is produced mainly by platelets. Moreover, a certain amount of caution is called for in interpreting these data, since renal prostaglandin clearance may not closely reflect changes in production.

Our results show that 2,3-dinor-6-keto-PGF1α is also significantly reduced in PIH as compared with normotensive pregnancy, while 2,3-dinor-TXB2 is not significantly different. We also found a significant correlation between arterial blood pressure and 2,3-dinor-6-keto-PGF1α in the two groups of pregnant women. There is thus an imbalance between vasodilator and vasoconstrictor factors, not only in the kidneys but also at the systemic level, the vasoconstrictor factor predominating. At the moment, the causes of this phenomenon are by no means clear. PIH may be defined as a condition characterized by prostaglandin deficiency. The reasons for this are unknown, but it probably is not a primary condition. One hypothesis might be that endothelial damage, or functional alteration, possibly caused by immune complexes, leads to inhibition of PGI2 synthesis without substantially altering TXA2 synthesis.

One of the most characteristic hemodynamic aspects of PIH is an increased vascular reactivity to angiotensin II.19 It is conceivable, then, that a reduction in PGI2 or the lack of a reduction in TXA2 (or both) may not only in themselves produce vasoconstriction but may also potentiate the hypertensive effect of catecholamines and angiotensin, as has been shown for PGE2.34 Recent data have indicated that low-dose acetylsalicylic acid may reduce the production of TXA2 in umbilical vein blood without interfering with PGI2 and may prevent development of the full clinical manifestations of PIH in pregnant women with increased sensitivity to angiotensin II.35,36 Although the pathogenesis of PIH remains something of a mystery, there is reason to believe that the PGI2 and thromboxane present in the
systemic vasculature constitute an important link in the chain of events leading to this condition.

Acknowledgments

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References

8. McGiff JC. Interactions of prostaglandins with the kallikrein and thromboxane A2 production but normal prostacyclin by the placenta in hypertensive pregnancies. Prostaglandins 1984;24:78-95
9. Ylikorkala O, Viinikka L, Ylikorkala M. Increased thromboxane A2 production but normal prostacyclin by the placenta in hypertensive pregnancies. Prostaglandins 1984;24:78-95
22. Makila UM, Viinikka L, Ylikorkala O. Increased thromboxane A2 production but normal prostacyclin by the placenta in hypertensive pregnancies. Prostaglandins 1984;27:87-95
32. Gallery EDM, Hunyor SM, Gyory AZ. Plasma volume contract: a significant factor in both pregnancy-associated hypertension (preeclampsia) and chronic hypertension in pregnancy. Q J Med 1979;192:593-602
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