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.

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 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 μmol/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 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 both the left-side recumbent (3 hours) and upright (2 hours) positions. Twenty-four-hour urine collections were used for determining excretion of prostanooids and kallikrein. Pains were taken to impress on subjects the importance of proper urine collection following the precise instructions given. The adequacy of 24-hour urine collection was judged on the basis of urinary creatinine and urinary volume. As a control group for the kallikrein and prostanooid determinations, we selected 15 age-matched normotensive nonpregnant women. None of these control subjects was taking oral contraceptives or any other kind of drug.

### Laboratory Procedures

PGE, and the urinary metabolites of PGI, and TXA were determined by radioimmunoassay. We took urinary excretion of 6-keto-prostaglandin F (6-keto-PGF), and thromboxane B (TXB) as indices of renal PGI, and TXA production; the indices used for the systemic production of PGI, and TXA were urinary excretion of 2,3-dinor-6-keto-PGF, and 2,3-dinor-TXB, respectively.

Urine samples were purified by means of chromatographic procedures before the assays. The method has been partly described previously. 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 [3H]-keto-PGF (150 Ci/mmol, Buckinghamshire, Amersham, UK) was then added to each sample. As a first chromatographic step, the urine samples were passed through Sep-Pak C 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 acetone/triethylamine (30:70; 300 μl; 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 octadeylsilane column was used (Hyperchrome ODS2, 15 × 4.6 cm, 5 μm; Bishoff, Leonberg, FRG). Prostaglandin and thromboxane metabolites were eluted isocratically with acetone/triethylamine (30:70; acidified to pH 3 with trifluoroacetic acid). Flow rate was 1 ml/min. Good separation of PGI, and TXA metabolites was obtained. Two fractions were collected, the first containing both 2,3-dinor-TXB, and 2,3-dinor-6-keto-PGF. These fractions were then dried, vacuum dried, and suspended in 0.02 M phosphate buffer, pH 7.4. The recovery of [3H]-keto-PGF, added to each sample was 28.6 ± 15% (mean ± SD) at the end of the purification procedure. Recovery rates in our laborato-

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**Table 1. Clinical Characteristics of Study Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>NP (n = 15)</th>
<th>PIH (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>28 ± 4</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Range (yr)</td>
<td>21–38</td>
<td>19–42</td>
</tr>
<tr>
<td>Gestational age at delivery (wk)</td>
<td>39 ± 1</td>
<td>37 ± 2*</td>
</tr>
<tr>
<td>Range (wk)</td>
<td>36–41</td>
<td>32–40</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3344 ± 318</td>
<td>2529 ± 1056</td>
</tr>
<tr>
<td>Range (g)</td>
<td>2850–3790</td>
<td>1090–4740</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td>571 ± 103</td>
<td>459 ± 177</td>
</tr>
<tr>
<td>Range (g)</td>
<td>380–760</td>
<td>160–800</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>114 ± 8</td>
<td>148 ± 8‡</td>
</tr>
<tr>
<td>Recumbent systolic</td>
<td>70 ± 2</td>
<td>98 ± 5§</td>
</tr>
<tr>
<td>Upright systolic</td>
<td>112 ± 10</td>
<td>147 ± 7§</td>
</tr>
<tr>
<td>Upright diastolic</td>
<td>79 ± 4</td>
<td>105 ± 42</td>
</tr>
</tbody>
</table>

Values are means ± SD. NP = normotensive pregnant women; PIH = women with pregnancy-induced hypertension.

* † ‡ § † † ‡ ‡ ± p < 0.002, † † ‡ ‡ p < 0.02, † † † ‡ ‡ ‡ p < 0.001, compared with values in the NP group.
ry are approximately 45% for PGE<sub>2</sub> and approximately 35% for the other compounds (subjected to the HPLC procedure).

Radioimmunoassay of 6-keto-PGF<sub>1α</sub> has been described elsewhere. Urinary TXB<sub>2</sub> and PGE<sub>2</sub> 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-PGF<sub>1α</sub>. This antisera has high cross-reactivity with 6-keto-PGF<sub>1α</sub> (about 100%), but low cross-reactivity with TXA<sub>2</sub> metabolites (<0.02%).

[3H]6-Keto-PGF<sub>1α</sub> (specific activity, 150 Ci/mmol; Amersham) was used as a tracer, and authentic 2,3-dinor-6-keto-PGF<sub>1α</sub> was used as the standard in the incubating mixture. For the radioimmunoassay of 2,3-dinor-TXB<sub>2</sub>, we used anti-TXB<sub>2</sub> sera produced by the Pasteur Institute, which also showed high affinity for 2,3-dinor-TXB<sub>2</sub>. [3H]TXB<sub>2</sub> and authentic 2,3-dinor-TXB<sub>2</sub> 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-PGF<sub>1α</sub> and 2,3-dinor-TXB<sub>2</sub> 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 radioimmunoassay of the angiotensin I generated. Urinary kallikrein excretion was determined by means of a slightly modified colorimetric method. 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 radioimmunoassay.

**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 left-side 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-PGF<sub>1α</sub> and PGE<sub>2</sub> in the PIH group (Figure 1). Equally, women with PIH showed a reduced excretion of PGI<sub>2</sub> systemic metabolites (Figure 2). On the other hand, urinary excretion of TXB<sub>2</sub> and 2,3-dinor-TXB<sub>2</sub>, the metabolite of systemic TXA<sub>2</sub>, 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-PGF<sub>1α</sub> 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 TXB<sub>2</sub> 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 PGE<sub>2</sub> and PGI<sub>2</sub> metabolites has been observed in normal pregnancy, and this phenomenon is thought to be related, at least hypothetically, to the cardiacoradiac changes characterizing this condition. 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 ± 2.6†</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, †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>PGE₂ (ng/24 hr)</td>
<td>179 ± 23</td>
<td>993 ± 243*</td>
<td>255 ± 55†</td>
</tr>
<tr>
<td>6-keto-PGF₁₀ (ng/24 hr)</td>
<td>239 ± 26</td>
<td>1407 ± 242*</td>
<td>726 ± 135*†</td>
</tr>
<tr>
<td>TXB₂ (ng/24 hr)</td>
<td>57 ± 8</td>
<td>121 ± 15§</td>
<td>91 ± 18</td>
</tr>
<tr>
<td>2,3-dinor-6-keto-PGF₁₀ (pg/mg creatinine)</td>
<td>220 ± 29</td>
<td>831 ± 174*</td>
<td>291 ± 55†</td>
</tr>
<tr>
<td>2,3-dinor-TXB₁ (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.¹⁹ 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 TXA₂ 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.²⁰ Accordingly, in our group of normal pregnant women, we found no correlation between PRA or urinary kallikrein and prostaglandin excretion. An alternative ex-
plation may be that hormonal regulation of prosta-
glandins 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,²¹ while both TXA₂ and prosta-
glandins have been shown to be produced in vitro by
all pregnancy-associated tissues.²² The data available
at this point, however, are discordant.²³
A marked alteration occurred in urinary excretion
of vasodilator compounds in PIH. Renal kallikrein, PGE₁, and 6-keto-PGF₁α were significantly reduced as com-
pared with levels in normotensive pregnancy, though
urinary 6-keto-PGF₁α was still higher than in nonpreg-
nant 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.,⁸ at least as far as
PGE₁ is concerned.
PGI₂ and thromboxane in the kidney exert opposite
effects on plasma flow and glomerular filtrate, particu-
larly in conditions characterized by hyperreactivity
of the renin-angiotensin system, as is the case in preg-
nancy.²⁴,²⁵ The increased production of PGI₂ in this condi-
tion 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 glo-
merular 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

\[ y = 110 - 0.026x \]
\[ r = -0.636 \]
\[ p < 0.01 \]
attention in view of the relationship of reciprocal positive action existing between the renin-angiotensin system and thromboxane in the kidney. 24 - 26 27 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 It would seem unlikely, however, that an increased intrarenal generation of angiotensin II is the main cause of the renal vasoconstriction occurring in PIH; it is much more likely that an imbalance between PGI2, PGE2, and kinins, on the one hand, and production of TXA2, on the other, may play a decisive role.

In PIH, plasma volume tends to show a marked reduction as compared with normal pregnancy, 22 with hemoconcentration, an increase in capillary permeability, 30 and an increase in peripheral resistance. 3, 6 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. By contrast, 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 and TXB2 is 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 and TXB2 in the two groups of pregnant women. There is thus an imbalance between 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 PGE1. 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
The authors thank Dr. Garret FitzGerald (Department of Pharmacology, Vanderbilt University, TN, USA) for the comparative measurements of dinor derivatives of prostanoids and Dr. Anthony Steele for his linguistic assistance in preparing this manuscript.

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