PATHOPHYSIOLOGY AND NATURAL HISTORY
HYPERTENSION

Decreased prostacyclin biosynthesis preceding the clinical manifestation of pregnancy-induced hypertension

DESMOND J. FITZGERALD, M.B., STEPHEN S. ENTMAN, M.D., KATHERINE MULLOY, R.N., AND GARRET A. FITZGERALD, M.D.

ABSTRACT Patients who develop pregnancy-induced hypertension exhibit a lesser increment in prostacyclin biosynthesis than healthy pregnant subjects. Whether this precedes the development of clinical disease and therefore may be important in the pathogenesis of pregnancy-induced hypertension or is a secondary event is unknown. We prospectively determined prostacyclin biosynthesis in pregnant subjects at risk of developing pregnancy-induced hypertension by use of noninvasive approach, measurement of the urinary metabolite 2,3-dinor-6-keto-prostaglandin F₁α. Patients were recruited at less than 20 weeks gestation. After delivery, patients were retrospectively allocated by use of preset criteria, to one of four groups: (1) pregnancy-induced hypertension (n = 12), (2) hypertension in labor (n = 22), (3) chronic hypertension (n = 9), and (4) normotension (n = 24). There was a significant increase in prostacyclin biosynthesis in all study groups during gestation. However, patients who developed pregnancy-induced hypertension exhibited a lesser increment and this difference persisted throughout gestation. These results are consistent with a pathophysiologic role for altered prostacyclin biosynthesis in women with pregnancy-induced hypertension. In addition, decreased prostacyclin formation identifies a population at risk of developing pregnancy-induced hypertension. Such information would assist the design of clinical trials of drugs, such as aspirin, that might prevent the development of this disease.


PREGNANCY may be complicated by elevated blood pressure or may exacerbate preexisting hypertension. The mechanism that underlies pregnancy-induced hypertension is unknown and it is possible that the rise in blood pressure is a manifestation of more than one pathologic condition.1,2 In a cross-sectional study we have previously demonstrated that excretion of 2,3-dinor-6-keto-prostaglandin (PG) F₁α, a major urinary metabolite of prostacyclin,3 is increased during normal gestation.4 This increment was much less pronounced in women whose pregnancies were complicated by hypertension.

Prostacyclin, the major cyclooxygenase product of arachidonic acid in vascular endothelium, is a potent vasodilator and inhibitor of platelet aggregation5 and stimulates renin production in the kidney.6 In normal nonpregnant subjects production of this eicosanoid is below the threshold for biological activity.3 However, in view of its enhanced production in normal pregnancy,4 prostacyclin may regulate blood pressure and platelet activity during gestation. Thus, a reduction in prostacyclin biosynthesis, either through its effects on vascular smooth muscle or by resulting in enhanced platelet activity, may play a pathophysiologic role in pregnancy-induced hypertension, which is associated with a rise in peripheral vascular resistance and increased platelet consumption.1,2 In addition, it may be of predictive value in women destined to develop this condition. This is important for a disease for which early intervention may prevent development.1 The present study was designed to determine whether an alteration in prostacyclin biosynthesis precedes the rise in blood pressure in pregnancy-induced hypertension and whether it is specific for this condition and therefore might be a useful predictor of the disease. To test these hypotheses we prospectively determined prostacyclin biosynthesis in patients at risk of developing
pregnancy-induced hypertension. In addition, we compared urinary excretion of 2,3-dinor-6-keto-PGF$_{1\alpha}$ with the angiotensin sensitivity test. Increased sensitivity to angiotensin has been shown to precede the development of pregnancy-induced hypertension and has been used as a method of predicting the disease. However, in selected populations the angiotensin sensitivity test has been found to be less useful, and animal studies show that it may be harmful to the fetus.

Methods

Study populations. The study group consisted of women attending the Obstetrics Clinic at the Vanderbilt University Medical Center. They were selected on the basis of having one of the following risk factors: age less than 18 years, primigravid pregnancy, black race, and/or history of pregnancy-induced hypertension. Only patients recruited at less than 20 weeks gestation were included in the study. Informed consent was obtained from all subjects and the protocol was approved by the Committee for the Protection of Human Subjects at Vanderbilt University. Twenty-four hour urine collections were made at 11 to 20 weeks gestation, at 20 to 28 weeks, and between 28 weeks and term. In a subset of our patient population, urine was also collected more than 6 weeks after delivery. Patients were instructed to avoid any medications, in particular cyclooxygenase inhibitors, for at least 10 days before the urine collection. To ensure compliance with this requirement, serum was obtained for analysis of thromboxane B$_2$ levels with each 24 hr urine collection. In no instance were low levels of urinary 2,3-dinor-6-keto-PGF$_{1\alpha}$ associated with decreased serum levels of thromboxane B$_2$.

Patients attended the obstetrics clinic at 2 to 4 week intervals where they were seen by their attending obstetrician and the study nurse. At each clinic visit, blood pressure was recorded in the sitting position with a standard sphygmomanometer. Phase 5 was recorded as the diastolic end point. Urine was tested for protein by Dipstick. Patients were retrospectively allocated to one of four groups based on preset criteria: (1) pregnancy-induced hypertension, (2) chronic hypertension, (3) hypertension in labor, and (4) normotension. Allocation by the criteria listed below followed review of the clinic notes by two obstetricians who were blinded as to the results of the biochemical analysis. Pregnancy-induced hypertension was defined as an increase in clinic systolic blood pressure of 30 mm Hg or diastolic blood pressure of 15 mm Hg or an absolute blood pressure of 140 mm Hg (systolic) and/or 90 mm Hg (diastolic) on at least two clinic visits or on two occasions 6 hr apart after 24 weeks gestation in patients with chronic hypertension.

Angiotensin sensitivity. Angiotensin sensitivity was determined in 18 patients from the main study group and in 15 additional subjects recruited at 28 to 32 weeks gestation after a 24 hr urine collection for determination of prostacyclin metabolites. All patients were normotensive at the time of testing. Patients were studied in the supine position after 30 min of rest during which blood pressure was recorded indirectly at 5 to 10 min intervals with a mercury sphygmomanometer. Fetal heart rate was monitored continuously by ultrasound and uterine activity was recorded by tonometry. Angiotensin (Hypertensin, Ciba) was infused intravenously at a starting dose of 1 to 2 ng/kg/min and the dose was increased in 50% to 100% increments every 5 min until diastolic blood pressure increased by more than 20 mm Hg or to a maximum dose of 48 ng/kg/min. The dose of angiotensin II required to increase diastolic blood pressure by 20 mm Hg was derived from the linear regression of blood pressure on the dose of infused angiotensin II.

Biochemical measurements. 2,3-Dinor-6-keto-PGF$_{1\alpha}$ was measured by a stable isotope technique with the use of negative ion, chemical ionization, gas chromatography–mass spectrometry as previously described. Briefly, 5 ng of deuterated internal standard was added to a 5 ml aliquot of urine. After extraction and back extraction under alkaline and acid conditions, the sample was derivatized as the methoxime, pentafluorobenzyl ester. After further purification by thin-layer chromatography, derivatization was completed by formation of the trimethylsilyl ether derivative. Quantitation was accomplished with a Hewlett-Packard 5980 instrument operated in the negative ion mode, monitoring m/z 586 for endogenous 2,3-dinor-6-keto-PGF$_{1\alpha}$, and m/z 590 for the deuterium-labeled internal standard. Repeated measurements of 2,3-dinor-6-keto-PGF$_{1\alpha}$ over three 24 hr periods 1 to 6 weeks apart in three normotensive pregnant women demonstrated little change from week to week, the coefficient of variation being 10.8 ± 0.7%. Serum thromboxane B$_2$ was determined by a modification of the method of Fitzpatrick et al. after incubation of 3 ml of whole blood in a glass test tube at 37°C for 45 min.

Statistical analysis. The data are expressed as the mean ± SEM. The groups were compared by nonparametric one-way analysis of variance, by the Kruskal-Wallis test, and subsequent linear contrasts or pairwise comparisons when appropriate. This approach involves no assumptions about the distribution of the variables analyzed. Linear regression of blood pressure on the dose of infused angiotensin was by the method of least squares.

Results

Seventy-eight patients entered the study, 11 of whom were poorly compliant or were lost to follow-up. Twelve patients developed pregnancy-induced hypertension and nine were classified as chronic hypertensives. Of the remaining subjects, 22 developed hypertension in labor and 24 were normotensive. The clinical characteristics of the patient groups are shown in table 1. There was no significant difference between groups with respect to age, parity, history of previous pregnancy-induced hypertension, or fetal weight. Although the ratio of black to white subjects was lower among chronic hypertensives, there was no significant difference with respect to race between the other three
TABLE 1
Clinical characteristics of the four patient groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (yr)</th>
<th>Race (black/white)</th>
<th>Nullipara (%)</th>
<th>Blood Pressure (mm Hg)</th>
<th>Fetal wt (pounds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>24</td>
<td>23 ± 1.0</td>
<td>14/10</td>
<td>38</td>
<td>111 ± 3.3/65 ± 1.8</td>
<td>7.29 ± 0.2</td>
</tr>
<tr>
<td>Hypertension in labor</td>
<td>22</td>
<td>22 ± 0.9</td>
<td>13/9</td>
<td>59</td>
<td>113 ± 2.5/68 ± 1.9</td>
<td>6.8 ± 0.33</td>
</tr>
<tr>
<td>Pregnancy-induced</td>
<td>12</td>
<td>25 ± 1.3</td>
<td>5/7</td>
<td>33</td>
<td>112 ± 3.9/61 ± 2.5</td>
<td>7.16 ± 0.43</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>9</td>
<td>26 ± 2.8</td>
<td>1/8a</td>
<td>38</td>
<td>137 ± 8.3/83 ± 4.7a</td>
<td>6.95 ± 0.32</td>
</tr>
</tbody>
</table>

Blood pressure is the peak at less than 20 weeks gestation.
a < .001 vs normotensive.

groups and no significant effect of race on biochemical indexes. Clinic blood pressure was higher in chronic hypertensives in the first trimester than in the remaining groups. However, there were no significant differences in blood pressure in the normotensive subjects and patients who subsequently developed pregnancy-induced hypertension on entry into the study.

Normotensive subjects and patients who subsequently developed hypertension in labor demonstrated the normal midtrimester decline in blood pressure measured in the clinic followed by a gradual rise in pressure toward term (figure 1). In contrast, blood pressure rose steadily throughout gestation with a pronounced rise in the last 4 weeks in patients who developed pregnancy-induced hypertension (figure 1). Only two patients with pregnancy-induced hypertension developed significant proteinuria (>2+ by Dipstick) and edema, and only one patient received antihypertensive medication; the remainder were managed conservatively by bed rest with or without early delivery. Intrauterine growth retardation, defined as birth weight below the 5th percentile for gestational age, was diagnosed in three cases. One developed pregnancy-induced hypertension and two had hypertension in labor.

Excretion of 2,3-dinor-6-keto-PGF\textsubscript{1α} was increased throughout gestation in all groups compared with that in normal nonpregnant subjects (p < .001; figure 2). This increase was evident at less than 20 weeks and was similarly elevated in samples collected as early as 11 weeks gestation. The excretion of 2,3-dinor-6-keto-PGF\textsubscript{1α} was significantly less in patients who de-

FIGURE 1. Peak blood pressure throughout gestation in normotensive women (n = 24), in patients with hypertension during labor (n = 22), and in patients with pregnancy-induced hypertension (n = 12).
developed pregnancy-induced hypertension compared with that in either normotensive subjects (p < .001) or patients who developed hypertension in labor (p < .005). This difference was evident at less than 20 weeks gestation, preceding the rise in blood pressure measured in the clinic. There were no significant differences in serum thromboxane B2 in normotensive women (251 ± 40 ng/ml) and patients with pregnancy-induced hypertension (250 ± 36 ng/ml) or patients with hypertension in labor (222 ± 23 ng/ml). Thus, the differences between groups with respect to excretion of 2,3-dinor-6-keto-PGF\textsubscript{1α} were not secondary to drug-induced changes in cyclooxygenase activity. Furthermore, in a representative subset of the main study group, there was no significant difference between patients with pregnancy-induced hypertension and normotensive subjects in their excretion of 2,3-dinor-6-keto-PGF\textsubscript{1α} after delivery (table 2), demonstrating that, like the clinical disease, the abnormality in prostacyclin biosynthesis occurs only in pregnancy and does not represent exaggeration of a chronic difference between the groups. In contrast to patients with pregnancy-induced hypertension, excretion of 2,3-dinor-6-keto-PGF\textsubscript{1α} in patients who developed hypertension in labor was not significantly different from that in normotensive pregnant women (figure 2). Similarly, elevated urinary metabolite levels were found throughout gestation in patients with chronic hypertension, including two patients who subsequently developed superimposed pregnancy-induced hypertension, and did not differ significantly from those in normotensive women or patients with hypertension in labor (table 2).

Angiotensin sensitivity was determined in 33 patients at 28 to 32 weeks gestation. Of these, six developed pregnancy-induced hypertension, 16 remained normotensive and 11 developed hypertension in labor. Angiotensin sensitivity was reduced in all three groups compared with the reported values for normotensive nonpregnant subjects (<8 ng/kg/min), the mean levels being 17.2 ± 3.8, 14.2 ± 1.7, and 27.4 ± 4.6 ng/kg/min, respectively. There was no significant difference between groups in their sensitivity to angiotensin II or their blood pressure at the time of study. In contrast, there was a significant (p < .001) difference between groups with regard to excretion of 2,3-dinor-6-keto-PGF\textsubscript{1α}, with lower levels being found in patients with pregnancy-induced hypertension (figure 3).

**TABLE 2**
Comparison of 2,3-dinor-6-keto-PGF\textsubscript{1α} excretion (pg/mg creatinine) during pregnancy and 6 weeks after delivery in a subset of the main study group.

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 6)</th>
<th>Chronic hypertension (n = 7)</th>
<th>Pregnancy-induced hypertension (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During pregnancy</td>
<td>958 ± 248</td>
<td>1811 ± 574</td>
<td>614 ± 210</td>
</tr>
<tr>
<td>After delivery</td>
<td>106 ± 20</td>
<td>228 ± 77</td>
<td>180 ± 58</td>
</tr>
</tbody>
</table>

The values during pregnancy represent the mean of sample obtained <20 weeks, 20 to 28 weeks, and 28 weeks to term.
increase prostacyclin metabolite Second, compared with keto-PGFI, a is enhanced in normotensive subjects and a sevenfold increase in patients with chronic hypertension (table 2).

Third, the findings demonstrate prospectively that a reduction in the excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} precedes the development of clinical disease and is indeed detectable in the first trimester. Finally, they suggest that depressed excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} is relatively specific for pregnancy-induced hypertension because it does not occur in patients with hypertension during labor or chronic hypertension even when the latter is complicated by a further increase in blood pressure during pregnancy.

2,3-Dinor-6-keto-PGF\textsubscript{1\alpha} is a major oxidative metabolite of prostacyclin in human urine. Excretion of this metabolite is linearly related to infused prostacyclin and is a specific, noninvasive index of prostacyclin biosynthesis in vivo. Thus, artifacts resulting from invasive sampling techniques and/or analytic errors are avoided. Increased excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} occurs under conditions in which there is enhanced biosynthesis of the parent compound, such as myocardial infarction and diffuse atherosclerosis. Enhanced excretion could also reflect altered metabolism of prostacyclin. However, the ratio of urinary 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} to 6,15-diketo-13,14-dihydro-2,3-dinor-PGF\textsubscript{1\alpha}, a metabolite representing an alternate pathway of prostacyclin metabolism, is unchanged during normal pregnancy or pregnancy-induced hypertension, so that preferential conversion to 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} is unlikely to occur. In addition, the increase in excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} during pregnancy is similar to that reported for 6-keto-PGF\textsubscript{1\alpha}, the nonenzymatic hydrolysis product of prostacyclin in plasma. These findings suggest that the increase in urinary 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} does not reflect altered metabolism of the parent compound.

The reason for the decrease in prostacyclin biosynthesis in the presence of pregnancy-induced hypertension is unknown. These studies demonstrate no difference between groups in the postpartum period, suggesting that the abnormality is not simply an amplification of a chronic abnormality in prostacyclin biosynthesis. Uterine and/or placental tissues are thought to contribute to the rise in prostacyclin formation that occurs with normal pregnancy. Umbilical vessels and placental tissue obtained from patients with pregnancy-induced hypertension have a diminished capacity to generate prostacyclin. Although this has been reported as an abnormality specific to this disease, a similar defect in the capacity of placental

Although urinary 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} in the normotensive women undergoing angiotensin sensitivity testing tended to be higher than in the main study group at the same stage of gestation, this difference was not statistically significant.

### Discussion

These studies extend the previous findings of altered excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} in pregnant women and those with pregnancy-induced hypertension. First, they demonstrate that excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} is enhanced very early in normal pregnancy compared with nonpregnant levels in the same subjects and remains elevated throughout gestation. Second, the gestational increment in excretion of this prostacyclin metabolite is diminished in pregnancy-induced hypertension. Thus, there was only a two- to threefold increase in excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} over postpartum levels in patients with pregnancy-induced hypertension compared with an eightfold increase in normotensive subjects and a sevenfold increase in patients with chronic hypertension (table 2).

2,3-Dinor-6-keto-PGF\textsubscript{1\alpha} is a major oxidative metabolite of prostacyclin in human urine. Excretion of this metabolite is linearly related to infused prostacyclin and is a specific, noninvasive index of prostacyclin biosynthesis in vivo. Thus, artifacts resulting from invasive sampling techniques and/or analytic errors are avoided. Increased excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} occurs under conditions in which there is enhanced biosynthesis of the parent compound, such as myocardial infarction and diffuse atherosclerosis. Enhanced excretion could also reflect altered metabolism of prostacyclin. However, the ratio of urinary 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} to 6,15-diketo-13,14-dihydro-2,3-dinor-PGF\textsubscript{1\alpha}, a metabolite representing an alternate pathway of prostacyclin metabolism, is unchanged during normal pregnancy or pregnancy-induced hypertension, so that preferential conversion to 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} is unlikely to occur. In addition, the increase in excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} during pregnancy is similar to that reported for 6-keto-PGF\textsubscript{1\alpha}, the nonenzymatic hydrolysis product of prostacyclin in plasma. These findings suggest that the increase in urinary 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} does not reflect altered metabolism of the parent compound.

The reason for the decrease in prostacyclin biosynthesis in the presence of pregnancy-induced hypertension is unknown. These studies demonstrate no difference between groups in the postpartum period, suggesting that the abnormality is not simply an amplification of a chronic abnormality in prostacyclin biosynthesis. Uterine and/or placental tissues are thought to contribute to the rise in prostacyclin formation that occurs with normal pregnancy. Umbilical vessels and placental tissue obtained from patients with pregnancy-induced hypertension have a diminished capacity to generate prostacyclin. Although this has been reported as an abnormality specific to this disease, a similar defect in the capacity of placental

![Angiotensin Sensitivity](image.png)
tissue to generate prostacyclin has been reported in patients with intrauterine growth retardation and in pregnant subjects with chronic hypertension.\textsuperscript{28} These latter studies suggested that the reduction in prostacyclin biosynthesis in pregnancy-induced hypertension might merely reflect placental insufficiency. In the present investigation, decreased formation of prostacyclin in vivo was demonstrable even in the presence of mild pregnancy-induced hypertension in the absence of any significant reduction in fetal weight, and was within the normal range for pregnant women in two patients in whom intrauterine growth retardation occurred. It should be noted, however, that the severity of the disease in our patients may be underestimated since all patients developing a significant rise in blood pressure were treated with bed rest, early delivery, or antihypertensive medication. Thus, in a longitudinal study such as this, severe forms of the disease are unlikely to develop.

Prostacyclin generation also rose normally in patients with chronic hypertension and in patients who developed hypertension during labor. An increase in blood pressure during labor is difficult to assess in view of the varying course and stress of delivery. Since such patients are often excluded in the definition of pregnancy-induced hypertension,\textsuperscript{1} they were considered separately in this study. Identification of hypertension in labor was based on normal blood pressure throughout gestation, an increase in blood pressure occurring for the first time while the patient was in labor, and the absence of other clinical findings. It is likely that many of these patients were merely exhibiting an exaggerated pressor response to stress and pain. Therefore, in contrast to studies of the vascular capacity to form prostacyclin, our results suggest that altered prostacyclin biosynthesis is a specific feature of pregnancy-induced hypertension.

The occurrence of altered prostacyclin biosynthesis early in pregnancies complicated by pregnancy-induced hypertension and the induction of similar pathologic changes and hypertension in pregnant rats by a diet deficient in polyunsaturated fatty acids\textsuperscript{29} implicate abnormalities in prostanoid formation in the genesis of the human disease. It has been postulated that since prostacyclin is a potent vasodilator,\textsuperscript{5} pregnancy-induced hypertension results from a relative deficiency of prostacyclin.\textsuperscript{27} An important finding in this study is that the reduction in prostacyclin biosynthesis in patients with pregnancy-induced hypertension long preceded the development of clinical signs. Thus, it does not appear to be the direct cause of the rise in blood pressure. This is not unexpected, since the rate of prostacyclin biosynthesis in normal pregnancy based on the rate of excretion of 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} is on the order of 0.5 to 1 ng/kg/min, which is just below the threshold (2 to 4 ng/kg/min) for a hemodynamic effect of infused prostacyclin.\textsuperscript{30} Alterations in prostacyclin biosynthesis, however, may alter vascular tone by modulating the response to other vasoactive compounds. While sensitivity to angiotensin II normally declines during pregnancy, women who subsequently become hypertensive become increasingly sensitive to this agent.\textsuperscript{7,8} Administration of cyclooxygenase inhibitors or a diet low in prostaglandin precursors abolished the decreased sensitivity to angiotensin II during normal pregnancy, suggesting that vasodilator prostaglandins such as prostacyclin might modulate the response of vascular smooth muscle to angiotensin II.\textsuperscript{31,32} However, indomethacin, and perhaps other nonsteroidal antiinflammatory drugs, possess direct vasoconstrictor properties that are independent of their ability to inhibit cyclooxygenase in human arterial beds.\textsuperscript{33} In addition, in this study we found no difference between normotensive subjects and patients with pregnancy-induced hypertension in their pressor response to angiotensin II, despite a difference in prostacyclin biosynthesis.

Alternatively, prostacyclin may play a role in pregnancy-induced hypertension through its effect on platelets. A reduction in prostacyclin biosynthesis may result in increased platelet activation, either systemically or in the uterine vascular bed, resulting in enhanced vascular tone through release of platelet vasoactive mediators\textsuperscript{34} or obstruction of the placental vasculature by platelet aggregates. Consistent with a role for platelets in this disease, platelet activation and turnover are increased by an unknown mechanism in pregnancy-induced hypertension.\textsuperscript{34,35} Furthermore, platelet inhibition by aspirin prevents development of the disease.\textsuperscript{36,37} The beneficial effects of aspirin, a cyclooxygenase inhibitor, may appear paradoxical in a disease characterized by diminished formation of prostacyclin. However, at the doses used, prostacyclin biosynthesis is largely unaltered.\textsuperscript{38} In contrast, marked cumulative inhibition of platelet thromboxane A\textsubscript{2} formation and subsequent inhibition of platelet activation would be expected with this regimen.\textsuperscript{38} Thus, the role of prostacyclin in the genesis of this disease is unclear but it appears likely that it is mediated by its effects on platelet activation.

Since the decrease in urinary 2,3-dinor-6-keto-PGF\textsubscript{1\alpha} occurs early in gestation, long before the development of clinical signs, it may be a useful biochemical marker of pregnancy-induced hypertension and
may be helpful in selecting groups of high-risk patients for interventions, such as aspirin, aimed at preventing the disease. For example, metabolite excretion of less than 400 pg/mg creatinine at 20 to 28 weeks gestation was associated with a 65% risk of developing pregnancy-induced hypertension. In contrast, application of demographic markers to identify a population at risk results in an incidence of 10% to 15%. In addition, urinary 2,3-dinor-6-keto-PGF$_{1\alpha}$ was a better predictor of pregnancy-induced hypertension than the previously used angiotensin sensitivity test. The absence of altered angiotensin sensitivity in our patients may be a reflection of the population studied, since the finding was initially described in a highly selected population of black teenage primigravid patients who were at high risk of developing the disease. Increased angiotensin sensitivity occurs less frequently, if at all, in less selected groups. Although examination of the excretion of the prostacyclin metabolite may be useful in identifying groups of high-risk patients, its predictive power in individuals is less certain. This would require the study of a larger population with a more easily applied method such as the radioimmunoassay techniques that have been developed for other urinary prostaglandin metabolites.

In conclusion, this study confirms the previous report of a reduction in prostacyclin biosynthesis in patients with pregnancy-induced hypertension and demonstrates that this abnormality is present throughout gestation. Thus, decreased prostacyclin formation long precedes the development of pregnancy-induced hypertension, consistent with a pathophysiologic role for altered prostacyclin biosynthesis in this disease.

References

5. Bunting SR, Gryglewski R, Moncada AS, Vane JR: Arterial walls generate from prostaglandin endoperoxides a substance (prosta
glandin X) which relaxes strips of mesenteric and coeliac arteries and inhibits platelet aggregation. Prostaglandins 12: 897, 1976
15. Brash AR, Jackson EK, Sagasse C, Lawson J, Oates JA, FitzGer-
ald GA: The metabolic disposition of prostacyclin in man. J Phar-
macol Exp Ther 166: 78, 1983
16. Roy L, Knapp H, Robertson RM, FitzGerald GA: Endogenous biosynthesis of prostacyclin during cardiac catheterization and an-
17. FitzGerald GA, Pedersen AK, Patrono C: Analysis of prostacyclin and thromboxane A$_2$ biosynthesis in cardiovascular disease. Circula-
tion 67: 1174, 1983
20. Barrow SE, Blair IA, Waddell KA, Shepherd GL, Lewis PJ, Dol-
ley CT: Prostacyclin in late pregnancy: analysis of 6-oxo-prosta-
23. Gerber JG, Payne NA, Murphy RC, Nies AS: Prostacyclin produc-
tion by the pregnant uterus in the dog may act as a circulating
24. Downing J, Shepherd GI, Lewis PJ: Kinetics of prostacyclin syn-
thetase in umbilical artery microsomes from normal and pre-
30. FitzGerald GA, Friedman LA, Miyamoto I, O’Grady J, Lewis PJ: A double blind, placebo controlled, cross-over study of prostacy-
31. Everett RB, Whorley RJ, MacDonald PC, Gant NF: Effect of prostaglandin synthetase inhibitors on the pressor response to angio-
32. O’Brien PMS, Broughton-Pipkin F: The effect of deprivation of prostaglandin precursors on vascular sensitivity to angiotensin II
37. Wallenberg HCS, Makovitz JM, Dekker JA, Rotmans P: Low dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primigravidae. Lancet I: 1, 1986
Decreased prostacyclin biosynthesis preceding the clinical manifestation of pregnancy-induced hypertension.
D J Fitzgerald, S S Entman, K Mulloy and G A FitzGerald

_Circulation_. 1987;75:956-963
doi: 10.1161/01.CIR.75.5.956

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/75/5/956

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/