**Preeclampsia — A State of Prostaglandin Deficiency?**

**Urinary Prostaglandin Excretion, the Renin-Aldosterone System, and Circulating Catecholamines in Preeclampsia**

Erling B. Pedersen, M.D., Niels J. Christensen, M.D., Poul Christensen, M.S., Peter Johanneisen, M.D., Hans J. Kornerup, M.D., Søren Kristensen, M.D., Jørgen G. Lauritzen, M.D., Poul P. Leyssac, M.D., Anna Rasmussen, M.D. and Mogens Wohlert, M.D.

**SUMMARY** Urinary excretion of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) and F\textsubscript{2\alpha} (PGF\textsubscript{2\alpha}), plasma concentrations of renin, aldosterone, norepinephrine (NE) and epinephrine (E) were determined during pregnancy, 5 days, 3, and 6 months after delivery in preeclampsia, normotensive pregnant, and nonpregnant control subjects. The PGE\textsubscript{2} was higher in normotensive pregnant control subjects than in nonpregnant subjects. In preeclampsia, PGE\textsubscript{2} was reduced to nonpregnant level. PGF\textsubscript{2\alpha} was the same in preeclampsia and in normotensive pregnancy, but elevated when compared to the normotensive nonpregnant control group. Plasma concentrations of renin and aldosterone were increased during pregnancy, but considerably less in preeclampsia than during normotensive pregnancy. NE and E were the same as in nonpregnant subjects during both hypertensive and normotensive pregnancy. All parameters were normal 3 months after delivery. There were no correlations between PGE\textsubscript{2}, PGF\textsubscript{2\alpha}, plasma concentrations of renin, aldosterone, NE, or E and blood pressure level in third trimester either in preeclampsia or in normotensive pregnancy. PGE\textsubscript{2} was positively correlated to plasma concentrations of renin. It is suggested that the lack of renal PGE\textsubscript{2} in preeclampsia might be responsible for the decrease in renal blood flow and sodium excretion. It is hypothesized that preeclampsia is a state of prostaglandin deficiency. The changes in the renin-aldosterone system may be secondary to changes in prostaglandin concentration both in preeclampsia and normotensive pregnancy.

(Hypertension 5: 105-111, 1983)

**KEY WORDS** • epinephrine • aldosterone • blood pressure • catecholamines • hypertension • norepinephrine • preeclampsia • pregnancy • prostaglandin • renin

The mechanism of blood pressure elevation in preeclampsia is unknown. Pregnancy-induced hypertension has been attributed to increased activity of the sympathetic nervous system,\textsuperscript{1} the renin-aldosterone system\textsuperscript{2-4} and recent reports\textsuperscript{5,6} have suggested a lack of vasodilator prostaglandins. There are, however, no systemic longitudinal studies with simultaneous evaluation of urinary prostaglandin excretion, the renin-aldosterone system, and sympathetic adrenergic activity in preeclampsia and normotensive pregnancy both before and after delivery.

In the present study we measured urinary excretion of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), prostaglandin F\textsubscript{2\alpha} (PGF\textsubscript{2\alpha}), plasma renin concentration, plasma aldosterone concentration, plasma norepinephrine (NE) and plasma epinephrine (E) in patients with preeclampsia and in normotensive pregnant and nonpregnant control subjects. The pregnant groups were studied during pregnancy and 5 days, 3, and 6 months after delivery. To reveal possible pressor or depressor mechanisms in preeclampsia, it was our purpose to study changes in these parameters, correlations between these parameters and blood pressure, and relationships between urinary prostaglandins, the renin-aldosterone system, and the sympathetic nervous activity.
Patients and Methods

Patients

Patients with arterial hypertension in pregnancy, normotensive pregnant control subjects, and normotensive nonpregnant control subjects were included in the study. Patients admitted for arterial hypertension in pregnancy were included in the study if blood pressure was higher than or equal to 140/90 mm Hg at three different determinations on at least two different days. Exclusion criteria were previously known hypertension, symptoms of liver, endocrine, or primary heart disorders, and medical treatment.

Patients who had preeclampsia if hypertension was not diagnosed before pregnancy and first occurred in the last trimester; blood pressure was below 140/90 mm Hg on examination at 3 and 6 months after delivery; proteinuria using conventional methods occurred in the third trimester; and proteinuria was absent on examination at 3 and 6 months after delivery. The group consisted of 16 patients with a mean age of 28 years (range 18–35) and with a mean blood pressure of 153/103 mm Hg (range 173–142/117–90). All had proteinuria detected using a routine method, minimal 1.2 g/day (range 0.2–5.5) and maximal 3.9 g/day (range 0.4–15.4). Mean gestational age was 36 weeks (range 29–41) and delivery in examination in pregnancy. Twelve were primipara and four delivered for the second time; caesarean section was performed in 10 patients. The average weight increase was 14 kg during pregnancy. Six patients received chlormethiazole intravenously for 2 to 3 days after delivery because of threatening eclampsia.14 Fourteen babies were alive, weight 2414 g (range 920–4000), length 46 cm (range 37–54), and two were still-borne (weight 700 and 940 g).

Pregnant control subjects were randomly chosen among patients admitted because of suspicion of abnormal fetal position or previous spontaneous abortion. Exclusion criteria were blood pressure elevation or proteinuria before, during, or after delivery; symptoms of kidney, cardiovascular, liver, endocrine, or cerebrovascular disorders; or medical therapy. The group consisted of 18 patients with a mean age of 26 years (range 17–30), and a mean blood pressure of 108/64 mm Hg (range 125–93/80–50). Mean gestational age was 40 weeks (range 37–42) at delivery and 6 months after delivery. Fifteen patients were primipara and two delivered for the second and one for the third time. Caesarean section was performed in two patients due to placenta previa and gluteal position respectively. The average weight increase was 12 kg during pregnancy. All children were alive, weight 3307 g (range 2840–4300), length 51 cm (range 47–56).

Nonpregnant control subjects were randomly chosen among patients admitted for sterilization, changing of intrauterine contraceptive devices, or white vaginal discharge without other signs of gynecological diseases. Exclusion criteria were the same as in pregnant control subjects. The group consisted of 19 patients with a mean age of 23 years (range 21–27) and a mean blood pressure of 109/66 mm Hg (range 123–87/80–53).

All patients gave their permission to participate in the investigation after having been informed of the nature and purpose of the study.

Methods

Urinary prostaglandins E₂ (PGE₂) and F₂α (PGF₂α) were measured by radioimmunoassays.15 Plasma renin concentration was measured by radioimmunoassay of angiotensin I16 and given in international units (uIU/ml) of plasma, an internal standard of human renin being used as reference. Plasma aldosterone concentration was determined by a radioimmunoassay17 with a slight modification of a previously described method.18 Plasma NE and E were measured by a double isotope derivative technique13 also slightly modified.14 Blood pressure was measured by a conventional sphygmomanometer technique; Phase V of the Korotkoff sounds was used for the diastolic pressure level. Nonparametric tests were used for the statistical analyses.15 Mann-Whitney's rank sum test and Wilcoxon's signed rank test were used for unpaired and paired comparison between two groups, and Kruskal-Wallis's test and Friedman's test were used for unpaired and paired comparison between more than two groups. Correlations were calculated by Spearman's test.

Patients were examined during pregnancy, 5 days, 3 months, and 6 months after delivery. Blood samples for determination of plasma renin concentration, aldosterone, NE, and E were taken at 9 a.m. after a fasting period of approximately 8 hours and after supine rest for 1 hour. Excretions of PGE₂ and PGF₂α were determined in urine collected for a 24-hour period the day before blood sampling. Blood pressure measurements were performed three times just before blood samples were taken.

Results

Prostaglandins

Figure 1 shows the individual data for PGE₂. The levels during preeclampsia in the third trimester and 5 days after delivery (82.1 and 98.1 ng/24 hours, medians) were considerably lower than in normotensive pregnant control subjects (265.0 and 161.1 ng/24 hours, p < 0.01 and p < 0.02 respectively), but only slightly above the nonpregnant control level (47.9 ng/24 hours, p < 0.05 for the third trimester and p < 0.01 5 days after delivery). Three months after delivery, PGE₂ in the preeclampsia group (54.2 ng/24 hours) and the normotensive pregnant group (76.3 ng/24 hours) did not deviate significantly from the nonpregnant group (47.9 ng/24 hours). Comparison within both the preeclampsia group and the normotensive pregnant group showed no significant differences between the levels of PGE₂ excretions in the third trimester and 5
PREECLAMPSIA — A STATE OF PROSTAGLANDIN DEFICIENCY? / Pedersen et al.

Figure 1. Urinary prostaglandin E₂ excretion (PGE₂) in preeclampsia (PRE), normotensive pregnant control subjects (NP), and normotensive nonpregnant control subjects (N) in the first (A), second (B), and third (C) trimester of pregnancy, 5 days (D), and 3 months (E) after delivery. Log scale. Medians indicated by horizontal lines. Significant differences between the pregnant groups: ***p < 0.01; **p < 0.02; and between the pregnant groups and the nonpregnant control groups: ***p < 0.01; *p < 0.05.

Figure 2. Urinary prostaglandin F₂α excretion (PGF₂α) in preeclampsia (PRE), normotensive pregnant control subjects (NP) and normotensive nonpregnant control subjects (N) in the first (A), second (B) and third (C) trimester of pregnancy, 5 days (D) and 3 months (E) after delivery. Log scale. Medians indicated by horizontal lines. Significant differences between the pregnant groups and the nonpregnant control groups: ***p < 0.01.

The PGE₂ excretions at these two examinations were significantly higher than 3 months after delivery (p < 0.02 for preeclampsia and p < 0.01 for normotensive pregnancy). The ratio between urinary excretions of PGE₂ and creatinine was changed in the same way as PGE₂.

Figure 2 shows the individual data for PGF₂α. The levels during preeclampsia in the third trimester and 5 days after delivery (1041.0 ng/24 hours and 892.5 ng/24 hours) did not deviate significantly from the normotensive pregnant control group (1721.0 ng/24 hours and 1280 ng/24 hours), but were clearly elevated when compared to the nonpregnant control group (430.6 ng/24 hours, p < 0.01 for both the third trimester and 5 days after delivery). Three months after delivery, PGF₂α in the preeclampsia group (593.8 ng/24 hours) and the normotensive pregnant group (384.3 ng/24 hours) did not deviate significantly from the nonpregnant group (430.6 ng/24 hours). Comparison within the preeclampsia group and the normotensive pregnant group showed no significant differences between the levels of PGF₂α excretions in the third trimester and 5 days after delivery. The PGF₂α excretions at these two examinations were significantly higher than 3 months after delivery (p < 0.01 for both preeclampsia and normotensive pregnancy). The ratio between urinary excretion of PGF₂α and creatinine was changed in the same way as PGF₂α.

Renin and Aldosterone

Figure 3 shows plasma renin and aldosterone concentrations. In the third trimester, plasma renin and aldosterone concentrations were significantly lower during preeclampsia than during normotensive pregnancy (plasma renin concentration, 98 uIU/ml vs 129 uIU/ml, p < 0.05; plasma aldosterone concentration, 0.91 pmole/ml vs 2.16 pmole/ml, p < 0.01), but elevated compared to the nonpregnant control subjects (plasma renin concentration, 28 uIU/ml, p < 0.01 and aldosterone, 0.40 pmole/ml, p < 0.01). Plasma renin and aldosterone concentration fell after delivery and were the same as in the nonpregnant control group 6 months after delivery. The increase in third trimester in percentage of the level 6 months after delivery was...
FIGURE 3. Plasma renin concentration (PRC) and plasma aldosterone concentration (PAC) in preeclampsia (•—•), normotensive pregnant control subjects (0—0—0), and normotensive nonpregnant control subjects (O) in the first (A), second (B), and third (C) trimester of pregnancy, 5 days (D), 3 months (E), and 6 months (F) after delivery. Means ± 1 SEM. Significant differences between the pregnant groups: ***p < 0.01; *p < 0.05; and between the pregnant groups and the non-pregnant control groups: #**p < 0.01.

lower during preeclampsia than during normotensive pregnancy (plasma renin concentration, 270% vs 360%, p < 0.05; aldosterone concentration, 160% vs 402%, p < 0.01).

Catecholamines

Norepinephrine and E were randomly determined in subgroups of the patients with preeclampsia (n = 15), the normotensive pregnant control subjects (n = 11), and the nonpregnant control subjects (n = 16). There were no significant differences in NE and E between preeclampsia and normotensive pregnancy in either the third trimester (NE = 0.13 ng/ml median, range 0.05–0.30, in preeclampsia, and 0.13 ng/ml, range 0.06–0.25, in normotensive pregnancy; and E = 0.03

ng/ml, range 0.00–0.13, in preeclampsia, and 0.02 ng/ml, range 0.00–0.07, in normotensive pregnancy) five days after delivery (NE = 0.14 ng/ml, range 0.06–0.54, in preeclampsia; and 0.12 ng/ml, range 0.08–0.18, in normotensive pregnancy; and E = 0.03 ng/ml, range 0.00–0.06, in preeclampsia, and 0.02 ng/ml, range 0.00–0.06, in normotensive pregnancy) or 3 months after delivery (NE = 0.15 ng/ml, range 0.06–0.22, in preeclampsia and 0.15 ng/ml, range 0.09–0.33, in normotensive pregnancy; and E = 0.02 ng/ml, range 0.00–0.07, in preeclampsia and 0.01 ng/ml, range 0.00–0.07, in normotensive pregnancy). The levels in both preeclampsia and normotensive pregnancy were the same as in nonpregnant control subjects (NE = 0.18 ng/ml, range 0.08–0.29, E = 0.02 ng/ml, range 0.00–0.09).

Blood Pressure

Blood pressure is shown in figure 4. As expected, both systolic and diastolic blood pressures were elevated in preeclampsia when compared to normotensive pregnancy in the third trimester (systolic = \( p < 0.01 \); diastolic = \( p < 0.01 \)). Six months after delivery, blood pressure was below 140/90 mm Hg in all patients who had suffered from preeclampsia; however, the average levels in these groups continued to be higher than in the normotensive pregnant group (systolic = \( p < 0.01 \), diastolic = \( p < 0.01 \)) and the non-pregnant control group (systolic = \( p < 0.01 \), diastolic = \( p < 0.01 \)).

FIGURE 4. Blood pressure (BP) in preeclampsia (•—•), normotensive pregnant control subjects (0—0—0), and normotensive nonpregnant control subjects (O) in the first (A), second (B), and third (C) trimester of pregnancy, 5 days (D), 3 months (E), and 6 months (F) after delivery. Means ± 1 SEM. Significant differences between the pregnant groups: ***p < 0.01; and between the pregnant groups and the non-pregnant control groups: ****p < 0.01.
**Urine Volume, Sodium Excretion and Creatinine Clearance**

Table 1 shows urine volume, sodium excretion, and creatinine clearance. There were no significant differences in urine volumes between preeclampsia and normotensive pregnancy, but the values varied considerably in both groups. Urinary sodium excretion was significantly lower \( (p < 0.05) \) during preeclampsia than in normotensive pregnancy. Creatinine clearance was reduced in preeclampsia compared to normal pregnancy \( (p < 0.05) \). In the latter group, creatinine clearance was significantly higher \( (p < 0.01) \) than in the nonpregnant group.

**Correlations**

There were no correlations between systolic or diastolic blood pressure, and PGE\(_2\), PGF\(_2\alpha\), plasma renin concentration, plasma aldosterone concentration, NE, and E in pregnancy and after delivery either in preeclampsia or normotensive pregnancy.

Plasma renin and aldosterone concentrations were positively correlated in nonpregnant control subjects \( (\rho = 0.576, n = 19, p < 0.02) \) and 6 months after delivery in normotensive pregnancy \( (\rho = 0.588, n = 18, p < 0.02) \) and in preeclampsia \( (\rho = 0.581, n = 13, p < 0.01) \), but not during pregnancy or 5 days after delivery. Plasma renin concentration was positively correlated to PGE\(_2\), but not to PGF\(_2\alpha\), in the third trimester in normotensive pregnancy \( (\rho = 0.516, n = 17, p < 0.05) \) and preeclampsia \( (\rho = 0.551, n = 15, p < 0.05) \). There were no significant correlations neither between PGE\(_2\), or PGF\(_2\alpha\), and aldosterone, NE, and E nor between plasma renin or aldosterone and NE or E.

**Discussion**

The results showed that in preeclampsia urinary excretion of PGE\(_2\), but not PGF\(_2\alpha\), was reduced down to the same level as in nonpregnant women. This contrasts to the considerably elevated PGE\(_2\) excretion in normal pregnancy. There was, however, some overlapping between PGE\(_2\) ranges in preeclampsia and normotensive pregnancy.

It has been proposed that the changes in the systemic hemodynamics during pregnancy could be attributed to changes in prostaglandin concentrations in the peripheral vascular bed. Total peripheral resistance is decreased and the vascular capacity increased in normotensive pregnancy because blood pressure is reduced in the last half of pregnancy and both cardiac output and plasma volume are higher than in nonpregnant subjects. Enhanced local concentrations of prostaglandins in the vessel walls in normal pregnancy are presumed to reduce vascular tonus and thereby the total peripheral resistance, an effect possibly mediated via cyclic AMP. Recently it has been shown that both maternal and fetal blood from normal pregnancy contained a higher level of prostacyclin (PGI\(_2\)) than blood from nonpregnant control subjects. Prostaglandin levels were increased in plasma in normal pregnancy compared to nonpregnant control subjects. Sensitivity to angiotensin II which is reduced in normal pregnancy was increased after dietary deprivation of essential fatty acids, presumably inducing prostaglandin deficiency.
In preeclampsia, cardiac output is unchanged and plasma volume is reduced compared to normotensive pregnancy. Thus, pregnancy-induced hypertension is evidently accompanied by an elevation in total peripheral resistance, the mechanism of which is unknown. In view of the evidence suggesting that the changes in systemic hemodynamics during normal pregnancy are mediated by an increase in peripheral vascular prostaglandin synthesis, it is tempting to suggest that a defect in prostaglandin synthesis or its regulation might be responsible for the increased vascular resistance in preeclampsia. Direct evidence for this hypothesis has until now been sparse, in part because prostaglandins are very labile substances and measurements difficult. However, in preeclampsia PG production was reduced in umbilical and placental vascular tissue, and in maternal subcutaneous and uterine vessels, and a lower PGI-like activity was found in amniotic fluid. Surprisingly the plasmatic activity of prostacyclin-stimulating factor was not low in patients with severe preeclampsia in contrast to late normotensive pregnancy; this has been seen as a compensatory phenomenon due to a decreased vascular prostacyclin synthesis in preeclampsia. Furthermore, in the present study the lower urinary excretion of PGE, in preeclampsia most probably reflects a defect in renal prostaglandin synthesis, because PGE, is rapidly destroyed in the systemic circulation and thus is not carried to the kidneys by arterial blood. Urine volumes were the same in preeclampsia and normotensive pregnancy, whereas renal PGE, synthesis is increased by angiotensin II, and it cannot be ruled out that the difference in PGE, excretion between preeclampsia and normotensive pregnancy is due to different degrees of stimulation by the renin-angiotensin system. In view of the available evidence at present, the changes in prostaglandin production are likely to be of pathogenetic importance for the development of preeclampsia.

Acknowledgments
The authors thank Karen Petersen and her associates, and Lisbeth Madsen, Lisbeth Mikkelsen, and Jytte Sorensen, for skillful technical assistance.

References
9. Leyssac PP, Christensen P. A study of the effect of stimulated endogenous prostaglandin synthesis on urine flow, osmolar
Preeclampsia -- a state of prostaglandin deficiency? Urinary prostaglandin excretion, the renin-aldosterone system, and circulating catecholamines in preeclampsia.
E B Pedersen, N J Christensen, P Christensen, P Johannesen, H J Kornerup, S Kristensen, J G Lauritsen, P P Leyssac, A Rasmussen and M Wohlert

Hypertension. 1983;5:105-111
doi: 10.1161/01.HYP.5.1.105

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/5/1/105

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/