Preeclampsia — A State of Prostaglandin Deficiency?

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

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SUMMARY Urinary excretion of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) and F\textsubscript{2a} (PGF\textsubscript{2a}), 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{2a} 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{2a}, 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{2a} (PGF\textsubscript{2a}), 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.

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Supported by grants from the Danish Medical Research Council and the Danish Heart Association.

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Received March 16, 1982, revision accepted August 12, 1982.
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 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) at delivery and 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. Fourteen babies were alive, weight 2414 g (range 920–4000), length 46 cm (range 37–54), and two were still-born (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 examination in pregnancy. Fifteen patients were primipara, 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 $E_2$ ($PGE_2$) and $F_{2\alpha}$ ($PGF_{2\alpha}$) were measured by radioimmunoassays. Plasma renin concentration was measured by radioimmunoassay of angiotensin I 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 radioimmunoassay method with a slight modification of a previously described method. Plasma NE and E were measured by a double isotope derivative technique also slightly modified. 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. 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 $PGE_2$ and $PGF_{2\alpha}$ 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 $PGE_2$. 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, $PGE_2$ 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 $PGE_2$ excretions in the third trimester and 5
days after delivery. The PGE_2 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 PGE_2 and creatinine was changed in the same way as PGE_2.

Figure 2 shows the individual data for PGF_2a. 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, PGF_2a 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 PGF_2a excretions in the third trimester and 5 days after delivery. The PGF_2a 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 PGF_2a and creatinine was changed in the same way as PGF_2a.

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 (O--O--O), 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 nonpregnant 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 nonpregnant control group (systolic = p < 0.01, diastolic = p < 0.01).

FIGURE 4. Blood pressure (BP) in preeclampsia (•-•-•), normotensive pregnant control subjects (O--O--O), and normotensive nonpregnant control subjects (△) 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 nonpregnant control groups: ***p < 0.01.
TABLE 1. Urine Volume (Uvol), Urinary Sodium Excretion (UNa), and Creatinine Clearance (Cr) in Preeclampsia (PRE), Normotensive Pregnant Control Subjects (NP), and Normotensive Nonpregnant Control Subjects (N), in the Third Trimester of Pregnancy (C), 3 Days (D), and 3 Months (E) after Delivery

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<td>UNa (mmole/24 hrs)</td>
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<td>Ccr (ml/min)</td>
<td>Median</td>
<td>105*</td>
<td>118†</td>
<td>116</td>
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Significant difference between the pregnant groups = *p < 0.05; and between the pregnant groups and the nonpregnant control subjects = †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 PGE₂, PGF₂α, 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 PGE₂, but not to PGF₂α, 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 PGE₂ or PGF₂α 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 PGE₂, but not PGF₂α, was reduced down to the same level as in nonpregnant women. This contrasts to the considerably elevated PGE₂ excretion in normal pregnancy. There was, however, some overlapping between PGE₂ 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 (PGI₂) than blood from nonpregnant control subjects. Prostaglandin levels were increased in plasma in normal pregnancy compared to nonpregnant control subjects. The PGE₂ infusion, but not PGF₂α infusion, reduced the blood pressure increase after angiotensin II infusion in pregnant rabbits and in pregnant women, and the 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 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 PG1 production was reduced in umbilical and placental vascular tissue and in maternal subcutaneous and uterine vessels, and a lower PG1-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; thus the difference in PGE, excretion does not seem to be related to volume changes. Since PGE has both vasodilator and natriuretic effects, the decrease in renal blood flow, glomerular filtration rate, and sodium excretion in preeclampsia could possibly be attributed to lack of renal PG1 and/or PGE compared to normotensive pregnancy. Our results could be seen as a local manifestation of a more general prostaglandin deficiency in preeclampsia, indirectly shown for the systemic circulation and more directly for the utero-placental circulation.

Sympathetic activity can be reliably evaluated by NE and E. In the present study there were no significant deviations in NE or E between preeclampsia or normotensive pregnancy and NE and E were not correlated to blood pressure. Thus blood pressure elevation in preeclampsia is not due to an abnormal elevation of circulating catecholamines.

Both plasma renin concentrations and plasma aldosterone concentrations were increased during normal pregnancy and also, but to a lesser degree, in preeclampsia. The lack of positive correlation between blood pressure and plasma concentrations of renin or aldosterone, and the fact that plasma renin and aldosterone concentrations were lower in preeclampsia, is an argument against a causal relationship between blood pressure level and the renin-aldosterone system, which has been suggested in other studies. Renin and aldosterone secretion are stimulated by an increase in sympathetic nervous activity, a decrease in renal blood flow, and a decrease in plasma volume. Since plasma catecholamines were normal and identical in preeclampsia and normotensive pregnancy, the suppression of plasma renin and aldosterone concentrations in preeclampsia compared to normotensive pregnancy could not be related to changes in circulating NE or E. Furthermore, the suppression of plasma renin and aldosterone concentrations in preeclampsia does not fit the fact that both renal blood flow and plasma volume are lower than in normotensive pregnancy. Animal experiments have shown that prostaglandins enhance renin release and also possibly aldosterone secretion.

In the present study, the high PGE, excretion in normotensive pregnancy, the lower PGE, excretion in preeclampsia, and the positive correlation between PGE, and plasma renin concentration suggest that changes in the renin-aldosterone system might be secondary to changes in prostaglandin production. However, 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.

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_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
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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