PLASMA RENIN ACTIVITY, BLOOD URIC ACID AND PLASMA VOLUME IN PREGNANCY-INDUCED HYPERTENSION

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Summary

Plasma renin activity (PRA), plasma aldosterone (PA), blood uric acid (BUA), plasma concentrations of catecholamines (Pcat) and plasma volume (PV) were measured simultaneously in 24 patients with pregnancy-induced hypertension (PIH). This hypertensive group was divided into labile (LH) and persistent hypertension (PH) groups according to the response of their blood pressure to home bed rest. Compared to normal theoretical values, PV was decreased in both hypertensive groups (LH = -7%; PH = -14%). Compared to a control group (C) of 16 normotensive pregnant women, PRA was higher in LH and lower in PH whereas PA was lower in both hypertensive groups. BUA was higher than in C in both hypertensive groups. No difference in Pcat was found between the three groups. In the PH group negative correlations were found between BUA and PRA, as well as between BUA and PV but no correlation between PRA and PV nor between Pcat and BUA were found.

In conclusion:

1. LH and PH are two pathophysiologically different entities in PIH.
2. In PH renin secretion is not appropriate to hypovolaemia and therefore not primarily involved in the pathogenesis of hypertension.
3. Hypovolaemia may play a role in the increase of BUA in PIH.

Introduction

Normal pregnancy is characterised by a plasma volume expansion and a stimulation of the renin-angiotensin-aldosterone system. During pregnancy-induced hypertension, plasma volume contraction has been demonstrated [1]. The
results of studies on the renin-angiotensin-aldosterone system are controversial. Compared with normal pregnancy, some authors describe a stimulation of the system [2], others no difference [3], but the majority describe an inhibition [4]. There are few studies of plasma volume, blood uric acid and the renin-angiotensin-aldosterone system during pregnancy-induced hypertension. We report the results of such a study.

Patients and methods

Twenty-four hypertensive pregnant women have been studied and compared with 16 normotensive pregnant women. Hypertension was detected in the obstetric outpatient clinic by finding a blood pressure greater than 140/90mmHg, twice after 10 and 20 minutes sitting at rest. In the hypertensive group, hypertension was discovered after 20 weeks and all were normotensive before pregnancy and two months after delivery. The hypertensive women were studied in the nephrological outpatient clinic as soon as possible after the discovery of hypertension, according to the same protocol as the normotensive controls:

No patients had received drugs for at least one month;

All were ambulatory on a normal salt diet (confirmed by urinary sodium excretion and lack of weight loss since first examination for hypertension;

All arrived, fasting, between 8–10a.m., with a 24 hour urine collection and were weighed;

A venous catheter was inserted into an antecubital vein, the patient being in the supine position;

Blood pressure was measured after 30 minutes of rest in the lying position and then the blood samples were taken.

We distinguished two groups of hypertensive pregnant women according to the outcome of blood pressure after home bed rest has been prescribed:

1. The persistent hypertensive group consisted of 17 pregnant women who were found hypertensive not only in the obstetrical outpatient clinic but also, at least once, in the nephrological outpatient clinic.

2. The labile hypertensive group consisted of seven patients who were found hypertensive in the obstetrical outpatient clinic but who were not hypertensive in the nephrological outpatient clinic.

There is no difference between the persistent hypertensive group, the labile hypertensive group and the control group as regards age (respectively 27.2 ± 1, 25.4 ± 0.4, 28 ± 1 years), parity ratio (respectively 9/8, 3/4, 9/7 primigravida/multigravida), duration of pregnancy (respectively 31.5 ± 1.7, 31.2 ± 2.2, 31 ± 1.6 weeks), weight gain during pregnancy (respectively 12.5 ± 4.7, 9.4 ± 1.4, 10 ± 1.1kg) and natriuresis (respectively <12.2 ± 0.7, 10.2 ± 2.3, 13.3 ± 1.1, ratio of sodium excretion to creatinine excretion). The weight before pregnancy was significantly higher in the persistent hypertensive group than the control
group (71.9 ± 3.7 versus 55.3 ± 2.4kg p<0.01). Mean arterial pressure is significantly higher at the first obstetrical examination in the persistent hypertension group and labile hypertensive group than in control group (respectively 116.1 ± 2.1, 111.6 ± 1.7 and 88 ± 3mm of Hg, p<0.01).

Methods

Blood samples handling

The blood samples for plasma renin activity (PRA) and aldosterone were taken into EDTA vacutainers put into ice and were centrifuged at 4°C within 30 minutes and then stored at -30°C, so that little cryoactivation could be expected. The samples for catecholamine measurement were taken into heparinised vacutainers and handled in the same way. The measurements were all made within three months so that deterioration of the samples was unlikely.

Analytical methods [6]

PRA was determined by the radioimmunoassay of angiotensin I; plasma aldosterone by radioimmunoassay; plasma catecholamines, epinephrine and norepinephrine by the radioenzymatic method of Da Prada; blood uric acid was measured by the method of Folin.

Plasma volume was determined by the Evan’s Blue dilution method. Once the first blood sample was taken, 10cc of a solution containing 25mg of Evan’s Blue was injected through the venous catheter. The patient was placed in left lateral lying position. Ten minutes later, a second blood sample was taken from the opposite arm. Concentration of Evan’s Blue was determined by spectrophotometric method. The results have been expressed in percentage of normal theoretical values determined by Smith and Yarbrough [5], according to body surface and duration of pregnancy.

Statistical method

Comparisons of the groups were made using the Wilcoxon’s test for non-paired data. Linear correlations were calculated with a small computer TI-55-II.

Results

The mean (± SEM) values of the various parameters observed in the three groups are summarised in Table I.

Plasma renin activity was significantly lower in the persistent hypertensive group than in control group and labile hypertensive group. Plasma renin activity was significantly higher in labile hypertensive group than in control group and persistent hypertensive group.

Plasma aldosterone values were significantly lower in the persistent hypertensive group and labile hypertensive group than in control groups (respectively 218 ± 52, 271 ± 58 and 533 ± 52pg/ml).
<table>
<thead>
<tr>
<th>Patients groups</th>
<th>Plasma concentrations of</th>
<th>Ratio</th>
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<tr>
<td></td>
<td>Renin activity (ng/ml/h)</td>
<td>Aldosterone (pg/ml)</td>
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<tr>
<td>Non-pregnant control (NPC)</td>
<td>0.7 ± 3</td>
<td>120 ± 180</td>
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<td>(normal range)</td>
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<td>Pregnant control (PC)</td>
<td>6.7 ± 0.5</td>
<td>533 ± 52</td>
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<td>n = 16</td>
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<tr>
<td>Persistent hypertensive group (PH)</td>
<td>4.7 ± 0.3</td>
<td>218 ± 52</td>
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<tr>
<td>n = 17</td>
<td></td>
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<tr>
<td>Labile hypertension group (LH)</td>
<td>12.2 ± 0.8</td>
<td>271 ± 58</td>
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<td>n = 7</td>
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<td>Comparison significance</td>
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<tr>
<td>PH vs PC</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
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<tr>
<td>LH vs PC</td>
<td>p&lt;0.01</td>
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<tr>
<td>PH vs LH</td>
<td>p&lt;0.01</td>
<td>NS</td>
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There was no significant difference for plasma epinephrine and norepinephrine in the three groups. Blood uric acid was significantly higher in the persistent hypertensive group and in labile hypertensive group than in control group (respectively 302 ± 16, 298 ± 9 and 240 ± 18μmol/L). There was no significant difference between the two hypertensive groups for their blood uric acid.

Plasma volume was decreased in the persistent hypertensive group and the labile hypertensive group (respectively -14.6 ± 3.2% and 7.2 ± 2.6%) compared to that of normal pregnancy. The difference between the two hypertensive groups however was not significant.

**Linear correlation studies**

There was a negative correlation between blood uric acid and plasma renin activity in the persistent hypertensive group (n = 17, r = 0.596, p<0.05), (Figure 1).

Plasma volume and blood uric acid were negatively correlated when all the hypertensive patients are considered (n = 22, r = 0.691, p<0.001) or when only the 17 patients with persistent hypertension are considered (n = 17, r = 0.695, p<0.01), (Figure 2).

There was no significant correlation between plasma renin activity and plasma volume.

**Figure 1**
Discussion

Two kinds of pregnancy-induced hypertension were distinguished according to the response of blood pressure to home bed rest, the persistent hypertensive group and the labile hypertensive group. The persistent hypertensive group had a lower PRA than control patients whereas the labile hypertensive group had higher PRA than controls. These differences of PRA in the various hypertensive and control groups have already been found in a previous study [6], and cannot be explained by differences in clinical details, salt intake or plasma volume.

In both hypertensive groups, plasma volume has been found reduced compared to normal theoretical values, in agreement with the study of Gallery et al showing that plasma volume is contracted in hypertension induced by pregnancy [1]. In
our study, this finding cannot be explained by salt restriction or diuretic therapy, since all patients had a normal salt intake and had not taken drugs for one month. In the labile hypertension group, plasma volume contraction is associated with a stimulation of the renin angiotensin system. In contrast, in the persistent hypertensive group, plasma volume contraction is associated with an inhibition of renin secretion. No correlation between PRA and plasma volume could be found in either group. The lack of negative correlation between PRA and volume in the group of persistent hypertension, suggests a maladaptation of the secretion of renin to the volemic stimulus.

There is an increase in blood uric acid in the two hypertensive groups compared with control pregnant patients. Hypertensive pregnancies are associated with a reduced fractional excretion of uric acid [7] of which there is no good explanation. The role of lactate excess has been advocated but has not yet been proved. In our study, a significant negative correlation was found between plasma volume and blood uric acid. Beaufils et al [7] found a correlation between the variations of blood uric acid and the variations of plasma volume in a sequential study but not between the direct values of these two parameters measured at the same time. The fact that in our study such a correlation was found with the direct values is probably explained by the way by which the plasma volume was expressed (the percentage of the theoretical volume) which is a function of the term of gestation and of the body surface. This correlation suggests that volume concentration may be responsible for the blood uric acid increase. However, since Beaufils et al found a reduction of plasma volume in intrauterine growth retardation without increase of blood uric acid, hypovolaemia per se cannot explain hyperuricaemia. The existence of a common factor which is able to reduce fractional excretion of uric acid and plasma volume is therefore postulated. Angiotensin and norepinephrine may be this common factor since Ferris et al [8] have shown that they both could induce a decrease of fractional excretion of uric acid. The lack of significant positive correlation between plasma norepinephrine and blood uric acid does not support the role of norepinephrine. The negative correlation between blood uric acid and PRA would at first glance tend to exclude a possible role of angiotensin in the elevation of blood uric acid. However, Symonds et al [9] have found a negative correlation between plasma renin activity and plasma concentrations of angiotensin II in pregnancy-induced hypertension, with higher concentrations of angiotensin II than in normotensive pregnant women, suggesting therefore a possible positive correlation of blood uric acid and angiotensin II. The discrepancy between high plasma concentrations of angiotensin II and low PRA may be explained by the release of angiotensin-like substance such as those reported to be released when uterine blood flow is reduced in pregnant dogs [10].

References

1 Gallery EDM, Hunyor SN, Gyory AZ. Q J Med 1979; 192: 593
Open Discussion

MANN (Heidelberg) Plasma volume was not measured in controls, but derived from data on a different population, which may slightly invalidate the findings.

FOURNIER We did not measure plasma volumes in controls because of ethical difficulties so we used the published data of Yarbrough*.

MANN Were these also derived from the Evans blue dilution technique?

FOURNIER Yes, of course we used data derived from the same technique as that used in our study.

DAL CANTON (Naples) I would like to emphasise that your results in women are in full agreement with our results in rats. You have found hypovolaemia and this may well have been caused by a greater natriuresis until a new steady state had been obtained. You would not see this because your women were in a steady state and they had a similar sodium excretion as normotensive patients. In your opinion is this hypovolaemia related to the higher incidence of toxæmia induced by hypertension in pregnancy?

FOURNIER You’re asking me if the hypovolaemia is just a consequence of the increase in blood pressure?

DAL CANTON Yes, I mean the hypovolaemia may be a cause of toxæmia.

FOURNIER Well it’s difficult to say from my data as we have no sequential data up to now. You may think that hypovolaemia, by stimulating some vaso-constricting factors, may induce the hypertension with hypovolaemia, but I have no data on that.

LEVER (Chairman) Are you asking whether there are not two different forms of hypertension but one which may be the precursor of the other, is that what you are saying?

* Smith RW, Yarbrough CJ. Am J Obstet Gynecol 1967; 99: 18
DAL CANTON  No, in my opinion there might be this sequence of events; greater natriuresis in essential hypertensive women with hypovolaemia lowering uterine perfusion, producing uterine ischaemia and consequently toxaeemia.

KLEINKNECHT (Paris) According to your results and data in the literature, do you recommend volume expansion in hypertensive pregnant women, and if so what will be the expected benefit especially for the fetus?

FOURNIER That's a very difficult question to give a good practical answer, because we do not have the data. I think the first thing to do would be to cautiously expand as much as possible the blood volume. In a situation where the vessels are vasoconstricted you may induce pulmonary oedema when you induce plasma expansion. In our experience this has been done, not by us but in other obstetrical clinics and we have had three cases of toxaemia with convulsion and two with pulmonary oedema and when we made a haemodynamic study we had an increase in pulmonary artery wedge pressure. I would caution about the use of plasma expansion in women with hypertension.

BIANCHI (Pisa) We have seen recently a positive correlation between serum uric acid and sodium lithium counter transport. As you know, serum uric acid is reabsorbed mainly in proximal tubules by a mechanism that is essentially similar to this type of counter transport mechanism. A suggestion that might explain your data could be that there is an increase in sodium excretion because of a defect in autoregulation and then a secondary increase in proximal tubular reabsorption in an attempt to counteract this effect, without succeeding because the final result is decrease in plasma volume. This increase in proximal tubular absorption per se may lead to an increase in serum uric acid. In this way you may explain both the negative correlation between the serum uric acid and plasma volume and the data relating to serum uric acid and proximal tubular reabsorption. It is just a suggestion.

DORHOUT MEES (Utrecht, The Netherlands) There was a striking discrepancy between your aldosterone and plasma renin. Could that be related to a decrease in progesterone which is known to have an anti-aldosterone action?

FOURNIER Yes, we have measured progesterone but there was no significant difference in the group.

PEDERSEN (Århus, Denmark) Do you think there is a problem in using plasma renin activity in evaluating the renin aldosterone system? I think there is a problem because the renin substrate is increased during pregnancy and your method is dependent on the substrate concentration. I think it would have been better to use plasma renin concentration or plasma angiotensin II for evaluating the system.

FOURNIER I think there has been a study which showed that the increase in substrate was the same in the control and in hypertensive patients, we have not measured substrate.
EL MATRI (Tunis, Tunisia) Please can you give further information about your cases? Were they only pregnancy-induced hypertension or hypertension with underlying glomerulonephritis?

FOURNIER None had proteinuria two months after delivery and only three of the 24 had proteinuria. The patients had pregnancy-induced hypertension.

EL MATRI In your cases you had low renin, had they been treated with beta-blockers?

FOURNIER No, they were all without treatment when we measured these parameters. They had never been treated.

EL MATRI In that case do you advise not treating patients with low plasma renin by beta-blockers?

FOURNIER The point is that beta-blockers act on hypertension not only by decreasing plasma renin. There is clinical data from an English group showing that atenolol, and also data from Glasgow with labetalol, showing that it is good for the pregnant woman and the fetus.