PLASMA RENIN ACTIVITY LEVELS IN NORMAL AND PREECLAMPTIC PREGNANCIES

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SUMMARY : Our aims were to determine the potential role of plasma renin activity (PRA) in prediction of preeclampsia, to study the relationship between PRA levels and gestational age, and to evaluate the correlation between PRA and blood pressure findings in preeclamptic pregnancies. PRA levels were measured by RIA in normotensive (n=9) and preeclamptic (n=10) pregnant women in their third trimesters. The mean (±SE) PRA levels in the normal and preeclamptic pregnants were 2.50±0.53 and 2.84±0.89 ng/ml/h, respectively, the slightly higher level in the hypertensive group being statistically non-significant. PRA levels demonstrated a strong, but non-significant correlation with gestational age in the preeclamptic subjects (r=0.56), but there was no relationship between PRA levels and mean blood pressure (MBP) in this hypertensive state. We therefore conclude that PRA level in preeclampsia does not decrease, but slightly increases, when compared with its measurements in normal pregnant subjects, and also that PRA does not contribute to the determination of high blood pressure in pregnancy-induced hypertension.

Key words : Plasma renin activity, pregnancy, preeclampsia.

INTRODUCTION

In normal pregnancy there is approximately 50% increase in the total extra cellular fluid and blood volumes, which are the result of approximately 900 mmol sodium retention (3,13). The degree of plasma volume expansion in normal pregnancy is significantly and positively correlated with fetal birth weight (3). There also exist profound peripheral arterial vasodilatation in normal pregnancy, which leads to a condition "sensed" as an under fill state, despite volume expansion to this degree (13). In preeclampsia, much research documents relative hypovolemia in comparison with normal pregnancy (3, 6, 8, 14), and these data suggest that preeclamptic pregnants "sense" this reduced plasma volume, since sodium retention in the face of intravascular volume contraction is an expected homeostatic renal response (3). In other words, reduced plasma volume is not appropriate for the vasoconstricted state of preeclampsia, and therefore "not sensed" as normal, thus leading to sodium retention in preeclampsia (3).

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In most studies, it has been reported that plasma renin activity (PRA) in preeclamptic pregnancies decreases, whereas the value in normal pregnants increases significantly, when compared with its measurements in normal non-pregnant subjects (1, 10, 15, 16). More recently, some authors have noted increments in both plasma renin activity and angiotensin levels in preeclampsia (4, 7).

The aims of this study were: 1) to determine the potential role of PRA in the prediction of preeclampsia; 2) to study the effect of gestational age on PRA levels in the preeclamptics; and 3) to evaluate the correlation between PRA levels and blood pressure findings in preeclamptic subjects.

MATERIALS AND METHODS

Nine normal pregnant women in their third trimesters were studied; they were selected from those admitted to Obstetrics and Gynecology Outpatient Clinics of Çukurova University Hospital for their periodic pregnancy examinations. Ten preeclamptic patients in their third trimesters were studied; they were selected from those admitted to the same hospital. All women

ranged in age from 18 to 39 years, and no evidence of renal and/or cardiovascular disorders was present. Since hypertension in the third trimester is defined as a blood pressure of 140/85 mmHg or greater that is sustained during repeated measurements for 6 hours (4), all selected preeclamptic women had blood pressures ≥140/85 mmHg, associated with proteinuria and edema. Normal pregnant subjects were between 30 and 39 weeks of gestation; preeclamptic women were between 27 and 39 weeks of gestation. None of the pregnants had any previous stillbirths. The clinical data of the pregnant groups are shown in Tables 1 and 2.

All of the women had been admitted to Çukurova University Hospital at least 2 days before the study was performed. The normal pregnant women were prescribed a diet consisting of approximately 170 meq/day of sodium, and the pregnants with preeclampsia were given about 120 meq/day of sodium. None of the women took any drugs before and/or during the study, other than iron or vitamin supplements.

The same examiner measured the blood pressure every 4 hours along 2 days, with a manual sphygmomanometer at the right brachial artery after the women had been kept in the sitting position for ≥15 minutes. On the study day, blood

Table 1: Clinical data on the 10 women with preeclampsia.

Patient no.	Age (years)	Weight (kg)	Gravidity	Parity	Abortus	Gestational the study (weeks)	BP[1] (mmHg)	MBP[2] (mmHg)
1	39	68	7	5	1	28	160/90	113.333
2	28	85	3	0	2	39	140/100	133.333
3	31	65	5	2	2	35	170/110	130.000
4	39	110	8	5	2	36	150/100	116.666
5	21	75	1	0	0	37	150/100	116.666
6	33	110	4	3	0	34	160/110	126.666
7	36	69	4	3	0	32	180/120	140.000
8	20	75	1	0	0	27	190/100	130.000
9	29	65	2	0	1	28	170/85	113.333
10	30	80	1	0	0	32	180/130	146.666

(1) Blood pressure at time of sampling
(2) Mean blood pressure

Table 2: Clinical data on the normal and preeclamptic pregnants (mean±SE).

	Age (years)	Weight (kg)	Parity	Gestational age at the study (weeks)	BP[1] (mmHg)		MBP[2] (mmHg)
					Systolic	Diastolic	
NP* (n=9)	25.44±1.86	68.33±1.28	0.67±0.29	35.78±0.08	116.67±2.89	72.22±3.24	87.04±2.69
PE** (n=10)	30.60±2.08 p=0.103	80.20±5.36	1.80±0.66 p=0.30	32.80±1.31 p=0.9	165.00±5.00	104.50±4.25	126.67±3.65

(1) Blood pressure at time of sampling
(2) Mean blood pressure
(*) Normal pregnancy
(**) Preeclampsia

pressures were evaluated by the same examiner as described above, and simultaneously, venous blood samples were collected in pre-chilled tubes (Becton Dickinson Vacutainer Systems, England) kept in crushed ice, and which contain sodium were taken in the morning, between 9.00-10.00 a.m. All blood samples were kept in crushed ice, and the plasma was separated without delay by centrifuge for 15 minutes at 4°C, using 1800-2000xg. Hemolyzed samples were not used for PRA evaluation. Plasma samples were stored at -70°C until RIA (radio immunoassay) would be performed. Thawing of the samples before the assay were carried out taking care that the temperature did not exceed 4°C. Repeated freeze-thaw cycles were avoided.

Angiotensin I coated-tube RIA was performed in two aliquots of the same sample, one incubated at 37°C for generation and one non-incubated; then, PRA (plasma renin activity) was calculated as ng angiotensin I generated/ml/h (Renctk P2721, Sorin Biomedica Diagnostic Division RIA kit, Italy). The PRA assay sensitivity was 0.13 ng/ml; intra-and interassay coefficients of variation were 7.5 and 7.7%, respectively.

Statistical evaluation was performed with Mann-Whitney U test and correlation-regression analysis (CSS Statistica). The values were expressed as the mean±SEM.

RESULTS

There were no significant differences in maternal age, parity or gestational age between preeclamptic patients and normal pregnants as determined by Mann-Whitney U test (Table 2).

PRA levels of 19 women in their third trimester of pregnancy were tested. PRA values of the pregnant women are shown in Figure 1.

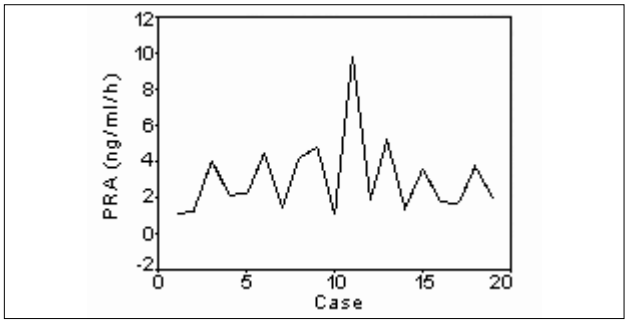

Figure 1: PRA values of the pregnant women. Cases from 1 to 9 are normal pregnants, cases from 10 to 19 are preeclamptics.

Table 3 shows the mean (±SE) values of plasma renin activity in the pregnant groups. Mean PRA values in the normal and preeclamptic pregnant groups were 2.50±0.53 and 2.84±1.89 ng/ml/h, respectively. Although mean PRA value of the preeclamptic pregnants was slightly higher than that of the normal pregants (Figure 2), this difference was found to be non-significant (p=0.81).

Table 3: Plasma renin activity (PRA) values in the pregnant groups.

PRA (ng/ml/h)	Normal pregnancy (n=9)	Preeclampsia (n=10)
Mean±SE	2.50±0.53	2.84±0.89
Minimum value	0.73	0.56
Maximum value	4.48	9.81
p=0.81		

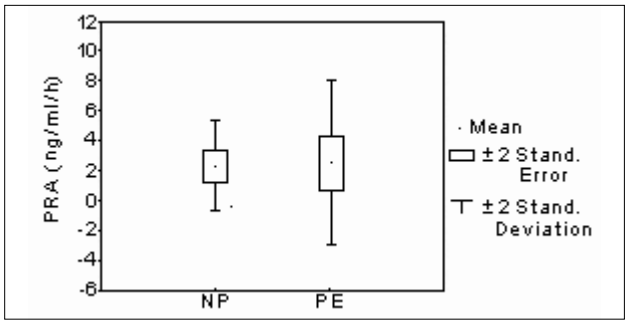

Figure 2: Mean values of PRA in the pregnant groups. PE: Preeclampsia; NP: Normal pregnancy.

There was no relationship between PRA levels and mean blood pressure (MBP) in the preeclamptic group (r=0.04, p=0.92), whereas a positive, non-significant slight correlation existed between PRA levels and MBP in the normal pregnants (r=0.18, p=0.64).

We demonstrated a slight, non-significant negative correlation between PRA levels and gestational age in the normal pregnants (r=-0.37, p=0.33); and a stronger non-significant positive correlation between PRA levels and gestational age in the preeclamptic subjects (Figure 3, r=0.56, p=0.09).

PRA levels correlated significantly and negatively with the maternal age in the normal pregnants (Figure 4, r=-0.77, p=0.02>0.05), but there was not a relationship between PRA levels and maternal age in the preeclamptic subjects (r=0.06, p=0.86).

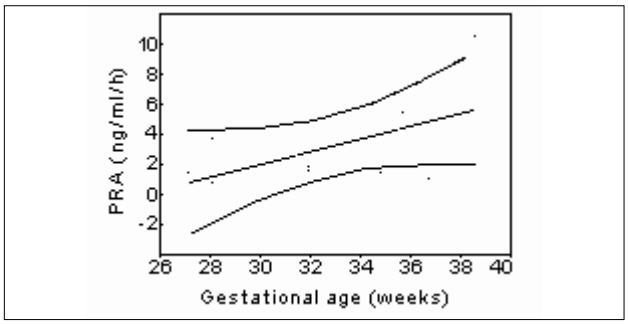

Figure 3: A strong, positive correlation exists between gestational age and the level of PRA in the preeclamptic subjects (n = 10, r = 0.56, p = 0.09).

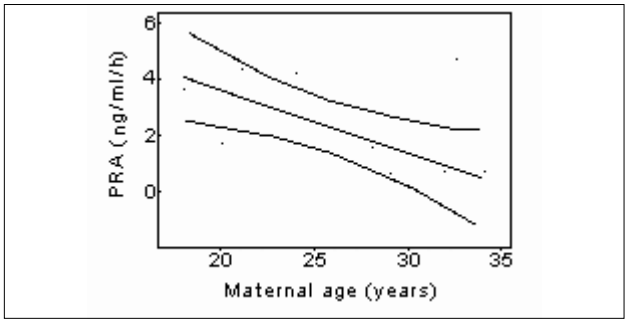

Figure 4: A significant, negative correlation exists between maternal age and the level of PRA in the normal pregnants (n = 9, r = -0.77, p = 0.02).

DISCUSSION

Mean PRA value in the preeclamptic subjects was found to be slightly higher than that of the normal pregnants (2.84 and 2.50 ng/ml/h, respectively), the difference being nonsignificant (Table 3, Figure 2). In most studies, it has been reported that plasma renin activity in preeclamptic pregnancies decreases, whereas the value in normal pregnants increases significantly, when compared with its measurements in normal non-pregnant subjects (1,10,15,16). More recently, some authors have noted increments in both plasma renin activity and angiotensin levels in preeclampsia (4, 7). Despite the increment in blood volume and extra cellular fluid volume, increased activity of the renin-angiotensin-aldosterone system is a characteristic of normal pregnancy, which is also associated with arterial vasodilatation. During normal pregnancy, expansion of intravascular space is so great that in spite of hypervolemia it causes a state of arterial under filling, which stimulates release of renin (3).

In the case of preeclampsia, there is early "over-expansion" of the plasma volume followed by "escape" from this positive sodium balance and consequent reduction of the plasma volume. Vasoconstriction is a dominant feature of preeclampsia, and plasma volume reduction is not appropriate for this vasoconstricted state. Therefore, preeclamptic subjects "sense" this reduced plasma volume, since sodium retention ensues as an expected homeostatic renal response (3).

Endothelial damage leads to pathophysiologic events that characterize preeclampsia, with resultant release of endothelin, which causes renal blood flow to decrease (12,13). So, decreased renal blood flow and "sensation" of reduced plasma volume in preeclamptic pregnancy may explain our finding that, mean plasma renin activity in preeclamptic patients is not decreased. Increased PRA levels may in turn lead to vasoconstriction in preeclampsia, by triggering release of angiotensin II. This conclusion is supported by Furuhashi *et al.*, who reported that angiotensin II was slightly higher in preeclampsia than in normal pregnancy (7).

In most studies, it has been reported that atrial natriuretic peptide (ANP) level is elevated in preeclampsia (2, 5, 6, 11), and it's known that ANP produces marked and sustained suppression of both renal renin secretion and plasma renin levels (9). Therefore, we conclude that increased ANP level in preeclampsia leads to suppression of PRA concentration, which otherwise would be elevated significantly due to marked plasma volume reduction in preeclamptic subjects.

The lack of correlation between PRA levels and MBP in the preeclamptic group (r=0.04), may suggest that the renin-angiotensin-aldosterone axis is not a determinant of high blood pressure in this hypertensive state. The positive, slight correlation between PRA levels and MBP in the normal pregnants (r=0.18) may indicate that increased blood pressure causing depression of renin release does not operate in normal pregnancy, and/or that increased PRA level causes blood pressure also to increase in healthy pregnants, by triggering angiotensin II, which is a potent vasoconstrictor agent. In fact, this explanation is in contrast to our established knowledge that there is unresponsiveness of vascular bed to angiotensin II during normal pregnancy (4).

The good relationship between PRA levels and gestational age in the preeclamptic subjects (r=0.56) indicates the existence of higher PRA values with advancing gestational age in preeclampsia; in contrast to this finding in preeclampsia, we found a slight, negative correlation between PRA levels and gestational age in the normal pregnants (r=-0.37), indicating that PRA level

tends to decrease, rather than increase in relation to gestational age during normal pregnancy.

Although there was not a relationship between PRA levels and maternal age in the preeclamptic subjects, PRA levels correlated significantly and negatively with the maternal age in the normal pregnants ($r=-0.77$, $p<0.05$); this finding suggests that lower PRA levels exist in elder, normal pregnant subjects. Peripheral arterial vasodilatation with relative under filling of the arterial circulation occurs in normal pregnancy, leading to stimulation of the renin-angiotensin-aldosterone axis, which contributes to the significant plasma volume expansion in normal pregnant subjects, and an adequate maternal plasma volume is at least one factor needed to maintain normal placental function and fetal growth (3, 13); therefore, our finding indicating lower PRA levels in elder, normal pregnant women may lead to the suggestion that fetal well-being is compromised in elder pregnants due to the inadequate plasma volume expansion resulting from lower levels of PRA.

The overall evaluation of our results yields to the conclusion that the relative hypovolemia of preeclampsia in comparison with normal pregnancy (3, 6, 8,14) is "sensed", leading to the existence of slightly increased, but not decreased PRA levels in this hypertensive state. Our data also suggest that PRA does not contribute to the determination of high blood pressure in pregnancy-induced hypertension.

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