Changes in plasmaconcentration of ANP and aldosterone in normal pregnancy and pregnancy complicated by pre-eclampsia

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Summary: Changes in plasmaconcentration of ANP in normal pregnancy and pregnancy complicated by pre-eclampsia were examined and compared to non-pregnant controls. The maternal plasma concentration increased gradually during normal pregnancy but values did not deviate significantly from non-pregnant women. A further increase was demonstrated post partum.

In pre-eclampsia maternal plasma ANP levels increased significantly compared with normal gravida at the same gestational age and non-pregnant controls. After delivery ANP decreased significantly. Non correlation between ANP and aldosterone were found in either normal pregnancy nor pregnancy complicated by pre-eclampsia.

It is not yet clear how important ANP is for the regulation of blood pressure and sodium and water balance during normal pregnancy and pregnancy complicated by pre-eclampsia.

INTRODUCTION

Atrial natriuretic peptide (ANP) is secreted by myocytes in response to inincrease in right atrial pressure ([1]). ANP has been shown to be involved in regulation of extracellular fluid volume and blood pressure ([2]). In addition to potent natriuretic and diuretic effects it causes arterial vasodilatation, lowers plasma-renin release and inhibits aldosterone release ([3]).

During normal pregnancy there is a significant increase in maternal blood volume ([4]) as well as an increase in glomerular filtration rate ([5]) and altered vascular sensivity to pressor hormones ([6]). The physiological role of ANP in these regulatory mechanisms during normal pregnancy is unknown. Several studies on the concentration of ANP in plasma (pANP) in normal pregnant women at different gestational ages has been performed, but the results are conflicting. Both increased and unaltered levels of pANP has been reported ([7–12]). An explanation for these conflicting results might be the great interindividual variation of the level of pANP, which by comparing groups could conceal a real difference, even if a relative large number of individuals are included in each group.

During pregnancy complicated by pre-eclampsia the concentration of renin and aldosterone in plasma (pAldo) are found to

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be reduced, but the mechanism for this suppression remain obscure ([13]). Since ANP has been shown to suppress both these hormones experimentally ([14]), one could expect a negative correlation between ANP and aldosterone in pre-eclampsia.

The purpose of the present study was to measure pANP and pAldo in the second and third trimester of normal pregnancy, the same women serving as her own control in order to avoid interferance from inter-individual variation. In addition pANP and pAldo levels in pre-eclampsia were compared with the levels in normal pregnancy at the same gestational age and a possible correlation between pANP and pAldo was evaluated. Non-pregnant age-matched women were used as controls.

MATERIAL AND METHODS

Normal pregnant women.

The group consisted of 11 women (median age 29, range 22-36 years) with uncomplicated singleton pregnancies. Four patients were primiparae, 4 delivered for the second time and 3 for the third time. All gave birth to healthy infants of average birth weight (median weight 3700, range 2950-3900 gm) for gestational age (median 40, range 37-42 weeks). All women were examined at 16th week of gestation, at 33-40th week of gestation and 1-5 days after delivery.

Pre-eclampsia.

Twelve patients (median age 26, range 21-35 years) were admitted for hypertension combined with proteinuria and/or oedema in the third trimester of pregnancy. Hypertension was defined as blood pressure higher than 140/90 on at least two different days after rest in hospital. Eight patients developed proteinuria (0.3 gm/l on more than one occasion and without associated urinary infection). The patients were normotensive and without proteinuria in the first and second trimester of pregnancy and again 3 weeks after delivery.

Patients excluded were those with suspected cardiac, hepatic or renal dysfunction, diabetes mellitus, multiple pregnancies, rhesus immunisation or patients receiving medical treatment before onset of hypertension. Each patient was investigated shortly after admission (median 38, range 35-40th week of gestation) and 1-5 days after delivery. All were primiparae. All babies were alive (median weight 2675, range 2107-4000 gm).

Controls.

The group consisted of 12 healthy, normal menstruating women. None were taking medication. Median age 31 (range 23-37 years).

All patients gave consent after having been informed of the nature and the purpose of the study. Venous blood was drawn after supine rest for 15 minutes and blood pressure measurements were performed just before the samples were taken. ANP samples were drawn into EDTA tubes, placed on ice and separated within 15 minutes. Plasma samples for ANP were stored at $-20°$ C.

Assay methods. Plasma concentration of ANP was measured according to the method described by Schütten *et al.* ([1]). Aldosterone was measured by radio-immunoassay.

Statistical analysis. Statistical comparison were made by Mann-Whitney rank sum test for unpaired data and Wilcoxon signed rank test modified by Pratt for paired data. Correlations were calculated by Spearman's test: Significance was at the level of $p<0.05$.

RESULTS

ANP. (Table 1).

In normal pregnancy a significant increase in plasma ANP concentration was seen from the second to the third trimester, but values did not deviate significantly from non-pregnant controls. At 16th week of

Table 1. – *Plasma concentration of ANP (pg/ml) during normal pregnancy and in pre-eclamptic women compared to non pregnant controls.*

	Number	Median	Range
NORMAL PREGNANCY			
16th week of gest.	11	12.3	0.6-105.4
33-40th week of gest.	11	15.9	6.1- 83.9
post partum	9	55.0	26.3-244.6
PRE-ECLAMPSIA			
35-40th week of gest.	12	35.9	12.7- 80.6
post partum	12	12.7	2.5-158.6
Controls	12	21.3	0.7-158.6

Table 2. – *Plasma concentration of aldosterone (pg/ml) during normal pregnancy in pre-eclamptic women and in non pregnant controls.*

	Number	Median	Range
NORMAL PREGNANCY			
16. week of gest.	11	345	150-450
33-40. week of gest.	11	870	570-<3000
post partum	9	150	90-660
PRE-ECLAMPSIA			
35-40. week of gest	12	435	156-<3000
post partum	9	138	78-780
Controls	12	171	63-270

gestation there was no difference in plasma ANP between back and lateral left recumbent position.

In pre-eclampsia ANP was significantly elevated compared to normotensive pregnant women at the same gestational age as well as compared to non pregnant control subjects.

In the puerperium ANP increased significantly in normotensive women and now differed significantly from controls. On the contrary, in pre-eclampsia ANP declined rapidly to normal values after delivery.

Aldosterone (Table 2).

Plasma concentration of aldosterone was significantly higher in normotensive pregnancy compared to non-pregnant controls. In pre-eclampsia the aldosterone level was increased compared to non-pregnant women, but significantly lower than in normotensive pregnancy. After delivery aldosterone were on normal levels in both normotensive pregnant and pre-eclamptic women.

Correlations.

There was no correlation between plasma concentration of aldosterone and ANP in either normal pregnant, pre-eclamptic or non pregnant women.

DISCUSSION

Our results indicate a significant increase of pANP from the second to the third trimester of normal pregnancy, although values did not deviate significantly from non-pregnant controls. In the early puerperium pANP increased significantly compared to non-pregnant controls.

Measurements of pANP during normal pregnancy have given conflicting results. Mean concentration of ANP are reported to be increased ([7, 8]), or unchanged ([9]) as opposed to non-pregnant controls. Where Otzuti *et al.*, suggested that there was an increase of pANP from the second to the third trimester ([10]) three subsequent studies were not able to detect any increase ([9, 11, 12]). A possible explanation for these contradictions may be found in the approach used for each study. ANP is influenced by many variables s.a. age, salt intake, samping time and/or posture of the patients. Furthermore a large individual variation of the concentration of pANP has been reported.

In the present longitudinal study the increase of ANP during normal pregnancy can be explained by the increase in blood volume and concomitant atrial distension. It may be pointed out that in this study gestational age was defined by ultrasound in early pergnancy. Consequently the observations obtained at the specified sampling time points may be valid with regard to the length of pregnancy.

The increased level of ANP in the early puerperium is in agreement with a previous report ([12]). The mechanism has to be clarified. ANP may help to mediate the compensatory increase in natriuresis and diuresis post partum in response to the relative volume loading at the parturition where the placental circuit is closed.

The increased level of pANP in pre-eclampsia is consistent with previous reports ([8, 10, 12, 15]). Futhermore our study showed that the level of ANP decreased simultaneously after termination of pregnancy in contrast to the increase of ANP seen in normal pregnancy. In one patient a sample was obtained in the 17th week of gestation before hypertension had developed. An increase of pANP of 30 times was seen after pre-eclampsia had developed (0.7 pg/ml - 21.7 pg/ml) although the value was still within the range of normal pregnancy.

The increased level of ANP in pre-eclampsia cannot be explained from our present knowledge of the mechanism of ANP release. Although the literature dealing with cardiac output and pulmonary capillary wedge pressure is variable, a study by Groenendijk *et al.* ([16]) indicates that pulmonary capillary wedge pressure is decreased in patients with pre-eclampsia. If this were the case low filling pressure would be associated with high level of ANP in pregnancy induced hypertension, which contrasts with the results in non-pregnant individuals. Factors other than atrial pressure may be involved in the regulation of natriuretic peptide in pregnant women with pre-eclampsia.

As in previous studies ([13]) our results confirm that aldosterone is elevated in normotensive pregnancy. The absence of an increase of blood pressure may be due to counteracting factors such as natriuretic effects of ANP.

The increased concentration of ANP in pre-eclampsia may contribute to the low level of aldosterone, as ANP has been shown to inhibit renin release and aldosterone secretion ([14]).

In conclusion the present study demonstrates that plasma concentration of atrial natriuretic peptide increases during normal pregnancy and increases to even higher levels in pregnancy complicated with pre-eclampsia. The pathophysiological and physiological role for ANP in normal pregnancy and pre-eclampsia, however, remain unsolved.

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