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DECREASED URINARY KALLIKREIN EXCRETION PRIOR TO DELIVERY IN PREGNANCY INDUCED HYPERTENSION

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Summary

Urinary kallikrein excretion was studied in 10 patients with pregnancy induced hypertension. One 24-hour urine sample was collected in 32–36 gestational weeks (preterm) and another one to five days prior to delivery after 37 full gestational weeks. Urinary kallikrein excretion (nanokatals/24 hours) was measured by using chromogenic substrate KABI S-2266. Mean urinary kallikrein excretion in preterm was 9.7±2.1 and prior to delivery 5.6±1.9. The decrease is significant ($p<0.02$). Prior to delivery urinary kallikrein excretion in pregnancy induced hypertension is significantly lower than in normotensive pregnancy (5.6 and 10.8, respectively, $p<0.02$) whereas in preterm the difference is not significant (9.7 and 12.7, respectively). Decreased urinary kallikrein excretion probably reflects changes in renal circulation caused by pregnancy induced hypertension. The decrease may also indicate disturbances in the interactions between renal kallikrein-kinin and other vasoactive systems.

Introduction

Renal kallikrein is a glandular-type kallikrein which is secreted by the distal tubule of the nephron. The urinary excretion of renal kallikrein correlates with the renal circulation and is decreased in essential hypertension [1]. Urinary kallikrein excretion increases during pregnancy but a controversy exists whether it is above the non-pregnant level throughout the normal pregnancy [2] or decreases from the high levels of the first and second trimester to the non-pregnant level in later pregnancy [3,4]. As in essential hypertension urinary kallikrein excretion is also decreased in pregnancy complicated by hypertension [4,5]. Hypertension during pregnancy is an exacerbation of underlying essential hypertension or is induced by pregnancy, then manifesting usually not before the late second trimester. Pregnancy induced hypertension with proteinuria and pre-eclampsia, is a syndrome peculiar to pregnancy [6]. We have studied urinary kallikrein excretion in late pregnancy in those patients with pregnancy induced

hypertension who were approaching delivery at term (after 37 full gestational weeks).

Clinical material and methods

Urine samples for kallikrein excretion were collected from pregnant women admitted to the obstetric clinic. The duration of pregnancy was estimated by the last menstruation and from the ultrasonical measurement of the biparietal measure between 17–19 gestational weeks. All patients were on free diet and were allowed to move freely. Urine samples from hypertensive patients were all collected during hospitalization. Patients with normotensive pregnancy were studied during routine visits to the maternity outpatient clinic or in the antenatal ward.

Pregnancy induced hypertension was defined as the elevation of blood pressure over 140/90mmHg in multiple measurements, first detected after the 24th/gestational week. Pre-eclampsia was diagnosed when hypertension presented with a daily proteinuria over 300mg. Patients with chronic hypertension, patients with hypertension developing in early pregnancy and patients with proteinuria only or any other sign of nephropathy were excluded.

The study group includes 10 patients with pregnancy induced hypertension. Their clinical data appear in Table I. One urine sample was collected between

TABLE I. Patients of the study group

Patient number	Age	Parity	Antihypertensive therapy	Proteinuria
1	20	1	–	+
2	27	1	–	–
3	20	1	–	+
4	34	2	–	–
5	25	1	+	+
6	40	1	–	–
7	24	1	+	+
8	28	1	–	+
9	30	1	–	–
10	26	1	–	+
	mean age 27.4			

32–36 gestational weeks (preterm) and another after 37 full gestational weeks one to five days prior to delivery. Two patient groups with normotensive pregnancy, one in preterm and another prior to delivery are characterized in Table II. Urinary kallikrein excretion of each normotensive group has been compared with that of the study group in the respective phase of gestation.

A single 24-hour collection of urine was taken at a time. The amount of urine

TABLE II. Patients with normotensive pregnancy

	32–36 gestational week (preterm)	Prior to delivery
Number	13	18
Mean age	31.3	28.2
Primipara	5	9
Multipara	8	9

was measured and an aliquot of mixed urine was kept at −20°C. The aliquot was thawed and centrifuged before the determination of kallikrein activity in the sample. Kallikrein activity was measured by using a chromogenic tripeptide substrate S-2266 (H-D-val-leu-arg-pNa-2HC1, Kabi Diagnostica, GMBH, Munich) according to the method of Amundsen et al [6]. Kallikrein releases enzymically a chromophore p-nitroaniline (pNa) from the substrate at a rate linearly increasing with the kallikrein concentration in the urine. Urinary kallikrein excretion is expressed as nanokatals of kallikrein activity in 24 hours.

Mean urinary kallikrein excretion has been given with one SEM. Student's 't' test for paired and unpaired samples was used for statistical calculations, p-value of 0.05 or less was considered significant.

Results

Figure 1 shows the urinary kallikrein excretion of the patients of the study group both in preterm and prior to delivery. Mean urinary kallikrein excretion in preterm is 9.2±2.1 and prior to delivery 5.6±1.9. The decrease is significant ($p<0.02$). In preterm urinary kallikrein excretion in pregnancy induced hypertension (9.2±2.1) does not differ significantly from that in normotensive pregnancy (12.8±1.4). Prior to delivery urinary kallikrein excretion is significantly lower in pregnancy induced hypertension (5.6±1.9) than in normotensive pregnancy (10.6±1.4) ($p<0.02$). In normotensive pregnancy urinary kallikrein excretion in preterm (12.8±1.4) does not differ significantly from that prior to delivery (10.6±1.4).

Discussion

Kallikrein activity in the urine is renal in origin and extrarenal kallikreins are not excreted, due to inactivation by the brush border epithelial cells of the proximal renal tubule [1]. This fact excludes the influence of placental or amniotic [7] kallikreins on renal haemodynamics during pregnancy. Concomitant to earlier studies [3,4] our study demonstrates the tendency, although reaching significance only prior to delivery, that urinary kallikrein excretion is lower in patients with pregnancy induced hypertension than in normotensive pregnancy during the third trimester. This finding is probably related to the changes in renal circulation caused by pregnancy induced hypertension.

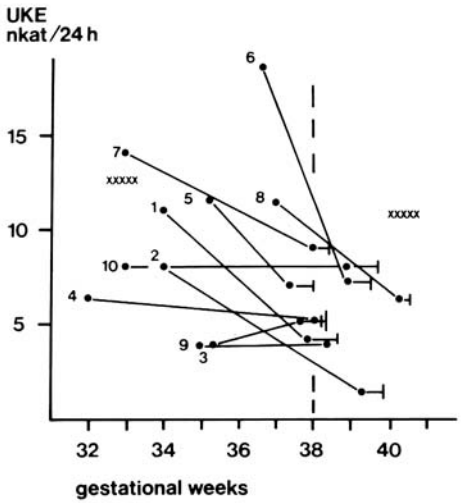

Figure 1. Urinary kallikrein excretion in the patients of the study group. The dots (••••) indicate the time of the urine sample collection between the 32–36 gestational weeks and prior to delivery. Vertical lines [|] show the date of delivery. Crosses (xxxx) show the means of urinary kallikrein excretion in a group of patients with normotensive pregnancy in the respective gestational phase

The observation that a further decrease of urinary kallikrein excretion occurs prior to delivery in pregnancy induced hypertension is interesting. Renal kallikrein is known to have extrarenal effects too [8], and it probably can contribute to the vasoactive kallikrein-kinin system of the circulation. Moreoever, the renal kallikrein-kinen system has interactions with renal prostaglandins [9] and the renin angiotensin system [10] which both act vasoactively. The response of these systems to pregnancy is altered in pregnancy induced hypertension [9,10] which alteration probably leads also to disturbances in their interactions. It remains obscure how such disturbances effect the various pathophysiological phenomena of hypertensive pregnancy, for instance the changes in the utero-placental blood flow. The remarkable decrease of urinary kallikrein excretion prior to delivery suggests that possible disturbances culminate by the time of delivery in pregnancy induced hypertension.

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