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Calcium and Phosphate Excretion in Preeclampsia

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Abstract: In preeclampsia, alterations in renal function, electrolyte and water metabolism are common findings. Recent studies have suggested that preeclampsia is associated with hypocalciuria. A total of 59 women were included in the present study, 15 of whom were nonpregnant (NP) healthy women, 20 normotensive pregnant women (NTP), and 24 pregnant women with severe preeclampsia (PEP). We compared the three groups in terms of calcium and phosphate excretion, and some parameters of renal function such as serum urea, creatinine and creatinine clearance. Urinary calcium and phosphate levels in the PEP group were significantly lower than in the NP group ($p< 0.001$ and $p< 0.01$, respectively) and NTP group ($p< 0.001$ and $p< 0.01$, respectively). The serum urea levels were higher in the PEP group than in the NP and NTP ($p< 0.001$) groups. The same pattern of increase in the PEP group was valid for serum creatinine concentrations as compared with the NP ($p< 0.01$) and NTP ($p< 0.001$) levels. The glomerular filtration rate measured by creatinine clearance was lower in preeclamptic women than in normotensive pregnant women ($p< 0.01$). Patients with preeclampsia had significantly lower ($p< 0.001$) excretion of calcium than the NP and NTP groups ($p< 0.001$). Likewise, the phosphate levels were lower in women with preeclampsia than in the NP and NTP groups ($p< 0.01$). There was no correlation between parameters of renal function and calcium or phosphate excretion.

Hypocalciuria and hypophosphateuria were found to be important features of severe preeclampsia and probably indirectly are related to the altered renal function seen in toxemia of pregnancy.

Key Words: Preeclampsia; calcium excretion; phosphate excretion; renal function

Introduction

Preeclampsia is a pregnancy-specific disease manifested by hypertension, coagulopathy, and impaired tissue perfusion. Its etiology remains unclear, and it is possible that the rise in blood pressure is a manifestation of more than one pathophysiological condition (1-4). One of these conditions is related to abnormal renal function (5-8) and probably decreased urinary calcium excretion (9-12).

Calcium and phosphate metabolism during normal pregnancy is characterized by minor changes in the serum levels of calcium and phosphate; however, urinary calcium and phosphate excretion increases (8,13). While urinary calcium values in nonpregnant women are about 100 - 250 mg/day, in pregnant women they range between 350 - 620 mg/day (8,14). Alongside the many studies reporting hypocalciuria in preeclampsia, there are others that have found no such correlation (15).

It is unclear whether the decrease of calcium is due to disordered renal function or is a compensatory mechanism in the pathogenesis of preeclampsia. The purpose of this study was to determine whether the calcium and phosphate excretion is lower in patients with preeclampsia, and what relation there is, if any, between calcium/phosphate excretion and the changed renal function seen in toxemia of pregnancy.

Material and Methods

The cases were divided into three groups: 15 nonpregnant (NP) healthy women (Control I), 20 normotensive pregnant (NTP) women with no disease (Control II), and 24 pregnant women with severe preeclampsia (PEP) (Study). Severe preeclampsia was defined as a blood pressure of ≥160/110 mmHg after 30 minutes of rest on two separate readings at least 6 hours apart with proteinuria (more than 300mg/day), and

edema. Liver enzyme levels of preeclamptic pregnant women were found to be in normal ranges. Preeclamptic and normotensive pregnant women were nullipara, and the gestational age was 33.25 ± 4.20 and 31.90 ± 5.89 weeks, respectively (Table1). Nonpregnant healthy women were 25-32 years of age. All women (Control I, II and Study groups) did not take any medication for at least 10 days prior the sample collection. Nonpregnant women were not on oral contraceptives and were in the follicular phase of the menstrual cycle at the time of sampling. Patients who had a history of hypertension before the 20th week of pregnancy, diabetes mellitus, or any renal disease were excluded from the study. All participants were on a free range diet. Twenty-four urine collections were taken from Control I, Control II and Study groups. Venous blood was obtained after overnight fasting at 10^{00} hours with each 24-hour urine collection, and centrifuged at 2000 g to remove the serum. Serum and urinary creatinine and urea levels were determined by the Jaffe and Kowarski methods, respectively. Creatinine clearance was then calculated. Urinary calcium and phosphate were determined by the Kramer-Tisdall and phosphomolibdic acid methods, respectively. Data are given as mean ± standard deviation. Student's t test and simple correlation analysis were used as statistical methods to test the results.

Results

Table 1 presents the gestational age and systolic and diastolic blood pressure values of normotensive and preeclamptic pregnant women.

Table 1. Clinical findings of normotensive pregnants (NTP) and preeclamptic pregnants (PEP)

	Gestationa Age(week)	Systolic Blood Pressure(mmHg)	Diastolic Blood Pressure(mmHg)
NTP(n = 20)	31.9 ± 5.89	115 ± 10.51	74 ± 6.8
PEP(n = 24)	33.25 ± 4.20	164.58 ± 20.79	104.79 ± 12.63
P	NS	p < 0.001	p < 0.001

Table 2 lists the renal function values in NP healthy, NTP and PEP women. Serum urea concentrations of the PEP group (23.08 ± 3.11 mg/dl) were significantly higher than those of the NP women (19.33 ± 1.44 mg/dl) and NTP ones (19.10 ± 1.51 mg/dl) (p< 0.001). The same pattern was seen in serum creatinine concentrations, which were significantly higher in the Study group (0.88 ± 0.17 mg/dl) than in the NP group (0.71 ± 0.18 mg/dl) (p< 0.01) and NTP group (0.69 ± 0.06 mg/dl) (p< 0.001). No significant difference was found between the urea and creatinine values of NTP women and those of NP ones. The creatinine clearance of PEP women (104.38 ± 29.63 ml/min) was lower than that of NTP women (126.20 ± 15.14 ml/min) (p< 0.01). However, there was no difference in comparison between the PEP and NP (113.04 ± 14.98 ml/min) groups. The creatinine clearance of normotensive pregnant women was higher than that of nonpregnant ones (p< 0.05).

Table 2. Renal function values in nonpregnant healthy (NP) women, normotensive pregnant women (NTP) and preeclamptic pregnant women (PEP)

(mg/dl)	Serum Urea (mg/dl)	Serum Creatinine (mg/dl)	Creatinine Clearance (ml/min)
NP (n = 15)	19.33±1.44	0.71±0.18	113.04±14.98
NTP(n = 20)	19.10±1.51	0.69±0.06	126.20±15.14
	$^{+}$NS	$^{+}$NS	$^{+}$p<0.05
PEP(n = 24)	23.08±3.11	0.88±0.17	104.38±29.63
	*p<0.001	*p<0.01	^{a}p<0.01
	^{a}p<0.001	^{a}p<0.001	

* Between PEP and NP

a Between PEP and NTP

\+ Between NTP and NP

Patients with preeclampsia had significantly lower excretion of calcium (92.14 ± 40.87 mg/l) than the NP (152.53 ± 25.60 mg/l) and NTP (171.80 ± 60.01 mg/l) groups (p< 0.001). Likewise, the phosphate levels (0.43 ± 0.38 g/l) were lower in women with preeclampsia than in the NP (0.80 ± 0.40 g/l) and NTP (0.76 ± 0.34 g/l) groups (p< 0.01).

There was no correlation between urinary calcium, phosphate and parameters of renal function.

Table 3. Urinary calcium and phosphate in nonpregnant healthy (NP), normotensive pregnant women (NTP) and preeclamptic pregnant women (PEP)

	Urine Ca (mg/l)	Urine P (g/l)
NP (n = 15)	152.53 ± 25.60	0.80 ± 0.40
NTP(n = 20)	178.8 ± 60.01	0.76± 0.34
	+NS	+NS
PEP(n = 24)	92.14± 40.87	0.43± 0.38
	*p<0.001	*p<0.01
	^{a}p<0.001	^{a}p<0.01

* Between PEP and NP

a Between PEP and NTP

\+ Between NTP and NP

Discussion

Preeclampsia can cause changes in virtually all organ systems, especially the cardiovascular, renal, hematological and immunological systems. The reason for these changes is unknown, but it is believed that they may be associated with an inadequate vasoactive prostaglandin synthesis (16-18), which can cause disorders of uteroplacental circulation (19), and renal tissue (5) and renal perfusion deffects (20). In association with these alterations renal blood flow and glomerular filtration rates decrease with the development of toxemia (20), which results in the decrease of urea and creatinine excretion (7). Similar to the reports of many investigators, in our study we also found serum urea and creatinine levels to be higher in preeclamptic pregnant women than in nonpregnant healthy women and normotensive pregnant women, while creatinine clearance values in preeclampsia were lower than in normotensive pregnant women.

Renal excretion of calcium and phosphate increases during pregnancy (8). Excretion usually increases during each trimester, with maximum levels reached during the third trimester. Proteinuria and alterations of phosphate and most notably calcium excretion are common findings of hypertension and some renal disorders in general. There is a decrease in urinary calcium levels in preeclampsia (9-12). Our findings in preeclampsia confirm the results of Sanchez-Ramos, Yoshida and Taufield (9-11). The reason for hypercalciuria in pregnancy is probably the increased glomerular filtration rate (11). Pedersen et al. reported that the fractional excretion of calcium in preeclamptic pregnant women was lower in the third trimester than it was in normotensive pregnant women (21). Because parathyroid hormone and calcitonin levels were not altered in the patients with preeclampsia, it was concluded that the differences in calcium metabolism were not related to alterations in the secretion of these hormones. Decreased renal filtration rate and increased tubular reabsorption of calcium and phosphate may result in hypocalciuria, and hypophosphateuria in toxemia. This may be a compensatory mechanism. Decreased calcium excretion may result in a slight but significant increase in serum levels, so that phospholipase A_2 is activated to stimulate impaired prostaglandin synthesis. It is reported that adaily supplement of 2000 mg calcium had significant results in lowering the incidence of toxemia (22). In addition, nonpregnant women with a calcium intake of at least 1000mg/day had a 20% lower risk of hypertension than women with an intake of less than 400 mg/day during four years of follow-up (23). These facts support our hypothesis.

Lower calcium excretion may result from dietary variation. All participants in our study were on a free range diet. Because we did not advise any of our patient to alter their diets, however, we believe it is unlikely that dietary calcium intake played an important role in our findings.

As a conclusion, hypocalciuria and hypophosphateuria are important features of severe preeclampsia and probably are indirectly related to the altered renal function seen in toxemia of pregnancy.

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