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Reduced urinary calcium creatinine ratio - can it be used as an early predictor of hypertensive pregnancies?

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Abstract

Introduction: Pregnancy induced hypertension (PIH) is a multifaceted syndrome with involvement of several important organs and it is associated with endothelial dysfunction. The results from many clinical studies show the relationship between the aggravation of the hypertensive complication and the change in concentrations of various chemicals in mother. Lowering of serum calcium and increase of intracellular calcium can cause an elevation of blood pressure in pre-eclamptic mothers. Hence in this study we propose to estimate urinary calcium-creatinine ratio, for early diagnosis of pre-eclampsia, with an intention to bring down maternal and fetal morbidity and mortality.

Methods: 50 hypertensive pregnant women and 50 age matched normotensive pregnant women were checked for their blood pressures, BMI and proteinuria by dipstick method. Sterile random mid-stream urine sample was used to estimate urinary calcium (OCPC method), urinary creatinine (Jaffe's method) and its ratio CCR. Cut off value for CCR was taken as ≤ 0.04.

Results: Amongst the cases, 84% of the patients had CCR ≤ 0.04, in contrast to 6% of controls with CCR ≤ 0.04. Chi square (χ^2) value was 58.34 showing that ratio is highly significant ($p<0.0001$).

Conclusions: A single random urinary CCR may be used as an effective tool for the early diagnosis of hypertensive pregnancy and may identify population at greater risk to be included in primary prevention programmes. In addition, early supplementation of hypertensive pregnant women with calcium may significantly reduce the morbidity and mortality.

Keywords: Urine, Calcium creatinine ratio, Hypertensive pregnancy, Pre-eclampsia, Early predictor

Introduction

Pregnancy induced hypertension (PIH) is a multifaceted syndrome with involvement of several important organs. PIH is also associated with endothelial dysfunction[1]. Pre-eclampsia is the development of high blood pressure (>140/90mm of Hg) with proteinuria, edema or both, induced by pregnancy usually after 20th week of gestation and sometimes earlier when there are extensive hydatidiform changes in the chorionic villi or multifetal pregnancy[2]. Pre eclampsia is a pregnancy specific disease and is one of the most common causes of maternal and fetal mortalities[3]. Its incidence is 4-8% of pregnancies[4]. Pre-eclampsia is resolved only on delivery[5]. The pathophysiological mechanism behind hypertensive pregnancy disorders is a failure of trophoblastic invasion of the spiral arteries, leading to maladaptation of maternal spiral arterioles, which may be associated with an increased vascular resistance of the uterine artery and a decreased perfusion of the placenta[6]. The precise cause of vascular endothelial dysfunction, an important factor in the pathophysiology of pre-eclampsia, remains unknown[7]. The results from many clinical studies show the relationship between the aggravation of the hypertensive complication and the change in concentrations of various chemicals in mother[8]. Lowering of serum calcium and increase of intracellular calcium can cause an elevation of blood pressure in pre-eclamptic mothers[9]. Hence in this study we propose to estimate urinary calcium-creatinine ratio, for early diagnosis of pre-eclampsia, with an intention to bring down maternal and fetal morbidity and mortality.

Materials and Methods

The current case-control study was carried out on 50 hypertensive pregnant women (between gestational ages 20-36 weeks) attending the antenatal clinic of a tertiary care hospital in Karnataka. Their ages ranged between 18-30 years. 50 age-matched normotensive pregnant women (controls) were involved in the study for comparison. The study protocol was approved by the institutional ethical clearance committee and informed consent was obtained from all the subjects. The cases were selected on the basis of simple random sampling method. All the participating women were checked for their blood pressures (by Sphygmomanometry – both Palpatory and Auscultatory methods), BMI (Quetelet's index → BMI = Weight in kg / Height in metre square) and proteinuria by dipstick method for labeling them as cases or controls. Those women with past or family history of pregnancy associated complication or other chronic diseases (such as chronic renal disease, chronic hypertension, molar pregnancy, intrauterine fetal death, urinary tract infection and twin pregnancy), those with history of vitamin D deficiency and those on drugs interfering with calcium levels such as thiazide group of diuretics, lithium etc. were carefully excluded from the study.

Under all aseptic precautions, 10ml of early morning random mid-stream urine sample was collected in calcium free sterile containers without preservatives. 0.2ml HCl was then added to prevent calcium salt precipitation and was immediately used after centrifugation to estimate urinary calcium (OCPC method - O-Cresolphthalein Complexone method), urinary creatinine (Jaffe's method) and its ratio (CCR), using Randox Daytona auto analyser. Urinary calcium-creatinine ratio (CCR) was calculated as: Urinary Calcium (mg/dl)/ Urinary Creatinine (mg/dl). Cut off value for CCR was taken as ≤ 0.04[10].

Principle of OCPC method for urinary calcium: In alkaline solution, the metal-complexing dye CPC forms a red chromophore with calcium, which is usually measured at a wavelength between 570 and 580nm[11].

Principle of Jaffe's method for urinary creatinine: Creatinine in alkaline solution reacts with picrate to form orange red coloured complex. The rate of formation of complex is proportional to the creatinine concentration, which is measured at 510nm[12].

Statistical analysis: Results obtained were expressed as mean ± SD. Statistical calculations were done using SPSS for windows (version 16) after applying chi square test and 't' test. P<0.05 was considered statistically significant.

Results

The study done was a case control study conducted on 100 pregnant women, comprising 50 hypertensive pregnant women as cases and 50 normotensive pregnant women as controls. In the study group 62% patients were primigravida.

Systolic blood pressure had a mean and SD of 157.06±16.23, 118.68±8.63 in cases and controls respectively, whereas diastolic blood pressure was 99.24±8.62, 73.82±4.12 in cases and controls respectively. Mean and SD of proteinuria (expressed in g/day) was found to be 0.35±0.14 and 0.14±0.03 in cases and controls respectively, with a p-value of <0.05.

Urinary calcium excretion in hypertensive group was found to be 3.7±1.89 mg/dl. It was compared with urinary calcium excretion in the control group (20.23±3.14). Similarly, urinary creatinine excretion in the hypertensive women was found to be 114.12±14.32 mg/dl. It was found to be lower than that in the controls (127.43±10.67 mg/dl).

Anthropometric, Clinical and laboratory characteristics of patients are presented in Table 1. The mean calcium-creatinine ratio in cases was 0.03 and that in controls was 0.16. Table 2 summarizes the percentage of subjects (under cases and controls) in terms of urinary calcium creatinine ratio (CCR). On comparison, 84% of the cases had CCR $\leq$ 0.04, in contrast to 6% of controls with CCR $\leq$ 0.04 [Table 2]. Chi square (χ^2) value was 58.34 showing that ratio is highly significant (p<0.0001).

Table 1: Anthropometric, Clinical and Biochemical characteristics of cases and controls

Parameters	Hypertensive pregnancy group (n = 50)	Normotensive pregnancy group (n = 50)	P value
Maternal age (yrs)	22.35±5.13	25.42±5.22	0.0038
SBP (mm Hg)	157.06±16.23	118.68±8.63	<0.0001*
DBP (mm Hg)	99.24±8.62	73.82±4.12	<0.0001*
Proteinuria (g/day)	0.35±0.14	0.14±0.03	<0.05
BMI (kg/m^2)	29.76±9.42	26.23±6.15	0.028
Urinary Calcium (mg/dl)	3.7±1.89	20.23±3.14	<0.0001*
Urinary Creatinine (mg/dl)	114.12±14.32	127.43±10.67	<0.0001*

(*)Highly significant

Table 2: Distribution of subjects with respect to urinary calcium creatinine ratio (CCR)

Group	CCR ≤ 0.04	CCR > 0.04
Hypertensive pregnancy group	42(84%)	8(16%)
Normotensive pregnancy group	3(6%)	47(94%)

Discussion

PIH and other hypertensive pregnancy disorders, representing a set of multifaceted syndromes are known to involve several important organs and are basically due to endothelial dysfunction[1]. Intracellular calcium levels alter during the course of a normal pregnancy as a result of its increased metabolism in vascular smooth muscle cells and these changes become even more complicated if the pregnancy is associated with hypertension[13]. A normal pregnant serum is known to amplify and pre-eclamptic serum to downregulate voltage dependent calcium channels. The exact cause of hypocalciuria in preeclampsia is unknown. It is thought to result from a differential combination of several factors such as decreased dietary calcium intake (which stimulates PTH release and concomitant increase in intracellular calcium levels, resulting in vascular smooth muscle contraction and thus hypertension[14]. reduced intestinal absorption, enchanced calcium uptake by placenta and fetus, or due to renal tubular dysfunction[1,15,16].

Normal pregnancy induces physiological body changes for coping with increased calcium demand by either increasing intestinal calcium absorption or by decreasing its renal loss. But when pregnancy is associated with high risk factors like hypertension and vasospasm, their renal excretion is further reduced together with concomitant increase in Ca^{++} reabsorption

by distal renal tubules[17]. So, we find a definite relationship between low urinary calcium creatinine ratio and risk for development of PIH.

In this study, hypertensive pregnant women had reduced urinary calcium levels compared to those of normotensive pregnancies and 84% of the hypertensive pregnant women had CCR ≤ 0.04. Our findings are in association with results of two age old studies, one done as early as 1988, evaluating the role of decreasing CCR and micro-albuminuria in prediction of preeclampsia, who came out suggesting them as screening tools in preeclampsia[18] and another study done in 1995, who predicted the importance of reduced CCR in a spot urine sample as it can be used as an effective marker for preeclampsia[1]. In one of the longitudinal studies done later on, authors reported similar finding in the third trimester of pre-eclamptic pregnant women and explained it on the basis of decrease in GFR due to pre-eclampsia associated severe vasospasm[19,20]. Few suggested increased distal renal tubular calcium reabsorption as a possible mechanism and few others say decreased fractional excretion as a reason[1]. Our study results also correspond with the results of many such similar studies which showed that calciuria in pre-eclampsia was significantly lower than in normal pregnancy[15,18,20,21].

The cut off value of CCR ≤ 0.04, considered in our study was similar to that of several other studies[2,22,23].

As with most of the studies, our study is not without controversies. Certain research groups observed increase in urinary creatinine in pre-eclamptic patients[24] and one of them found a limited value of CCR in predicting preeclampsia[25].

Nevertheless, estimation of calcium creatinine ratio in a random urine sample is a simple non-invasive test, which could be done easily on an OPD basis and it also ensures good patient compliance. Further, it can be done at a very reasonable price. It can therefore be routinely used for early diagnosis of hypertensive pregnancy disorders after 20 weeks of gestation. Early recognition of such complicated cases further helps in minimization of maternal and fetal morbidity and mortality.

Conclusion

Many tests to predict hypertensive pregnancies beforehand are coming up. Present study was devised to know the usefulness of urinary CCR in identifying at-risk patient. The present study showed lower urinary calcium excretion and CCR in hypertensive pregnant women than normotensive pregnant women. In subjects, 84% of the cases had urinary CCR ≤ 0.04. On statistical analysis, it was found that when CCR alone was taken as a high risk factor for the early diagnosis of hypertensive pregnancy, it was highly significant with a p value < 0.001. So, this test forms a satisfactory basis for the early diagnosis of pre-eclampsia.

Therefore, a single random urinary CCR may be used as an effective tool for the early diagnosis of hypertensive pregnancy. In addition, early supplementation of hypertensive pregnant women with calcium may significantly reduce the morbidity and mortality.

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Conflict of Interest

None

Source of Support

Nil

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