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THE PREDICTION FOR THE SEVERITY OF PREECLAMPSIA IN PREGNANT WOMEN BY THE EVALUATION OF URINARY CALCIUM/ CREATININE RATIO

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Abstract
Background: Preeclampsia, a hypertensive disorder in pregnancy, affects 2%-8% of pregnancy complications worldwide. Severe internal vasospasm causes renal changes, leading to hypo calcemia and proteinuria. Early diagnosis involves urinary calcium/creatinine levels.
Aim of the Study: To evaluate Urinary Calcium/Creatinine ratio in pregnant women with preeclampsia and to check it's association with severity of the disease.
Patients and Methods: This prospective case-control study was carried out on pregnant women admitted to labor room at Duhok Hospital for Obstetrics and Gynecology from 1st of March to 1st of September 2023, 150 pregnant women participated in this study at third trimester of pregnancy were consecutively divided into 3 groups: a group of women with preeclampsia, women with pregnancy-induced hypertension, and a control group of normotensive pregnant women, and 50 pregnant women for each groups. The calcium/creatinine ratio was estimated and the statistical analysis was done.
Results: There was a significant statistical difference among the studied groups regarding the mean maternal age; as it was significantly higher in pregnancy-induced hypertension group than the other two groups (P=0.001). The urinary calcium/creatinine ratio was significantly lower among the preeclampsia (P=0.019) than the control group only.
Conclusions: The urinary calcium/creatinine ratio showed lower mean levels in preeclampsia groups compared to control, suggesting it may predict preeclampsia but not detect its severity.
Keywords: Preeclampsia, Pregnancy, Urinary Calcium and Creatinine, Urinary Calcium/Creatinine Ratio, Pregnancy Induced Hypertension, Serum Creatinine.

Introduction

Preeclampsia (PE) is a severe hypertension disorder in pregnancy involving multiple organ systems, diagnosed by systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 6 hours apart after 20 weeks of gestation. [(1)]. Other clinical findings may include proteinuria, end-organ damage, impaired liver function, persistent right upper quadrant pain, new-onset headache, pulmonary edema, or renal insufficiency with abnormal laboratory values. Preeclampsia complicates about 20% of pregnancies in women with chronic hypertension [(1, 2)].
Preeclampsia, defined by the American College of Obstetrics and Gynecology (ACOG), is a condition characterized by hypertension and proteinuria after 20 weeks of gestation in a normotensive patient. However, many women develop systemic manifestations before proteinuria is detectable, leading to delayed diagnoses. The ACOG's hypertension 2013 task force revised the definition of PE to include severe features with or without proteinuria and exclude proteinuria as a criterion of severe features [(3, 4)]. The ACOG committee opinion issued in 2015 and reaffirmed in 2017 does not recommend screening

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to predict preeclampsia beyond obtaining an appropriate medical history. Because of the lack of adequate screening methods and the severe sequelae of the disease, all women suspected of preeclampsia undergo resource intensive testing, often requiring several-day hospitalizations for further investigation. Other methods of screening have been investigated, including a metabolomic pathways and combined metabolomic-proteomic data approaches [5, 6].

Renal changes in PE can be caused by severe internal vasospasm, leading to GFR decline and hypocalcemia. Proteinuria is linked to glomerular renal endothelins, a manifestation of widespread endothelial damage. Urine calcium excretion increases during pregnancy, due to increased renal GFR and renal calcium excretion [4-6]. However, renal ionized calcium excretion decreases in preeclampsia. Studies have investigated methods and tests based on calcium metabolic changes for early diagnosis or prediction of PE. Studies show that renal calcium extraction decreases with PE development, and urinary calcium excretion decreases with pregnancy-related hypertensive disorders [7, 8]. The current study aimed to evaluate the calcium, creatinine in urine, and urinary CCR ratio in pregnant women with preeclampsia and also to check the association of urinary CCR ratio with the severity of the disease.

Material and Methods

Study Design , Setting, and Data Collected Time: In this prospective case-control study, pregnant women who participated in the study included 150 pregnant women. It was carried out on women admitted to the ward or labour room at Duhok Hospital for Obstetrics and Gynecology from 1st March to 1st September 2023. Pregnant women >18 years old age, at 3rd trimester gestational age who agreed to participate in the research were included in the study. For statistical significance and comparison, these were divided into three groups:

Group1: The study involved 50 patients with PE who had blood pressure ≥140/90 mmHg twice after 20 weeks of gestation and proteinuria-tested with Dipstick ≥1+ dipstick in urine. Preeclampsia was diagnosed using NICE guideline criteria, including clinical features, blood pressure (Bp) measurements, and laboratory investigations.

Group 2: consisted of 50 patients with PIH who had Bp ≥140/90 mmHg on two occasions with 6 hours apart after 20 weeks of gestation and proteinuria-tested with Dipstick < 1+ dipstick in random sample of urine.

Group 3: The study included 50 normotensive pregnant patients without risk factors for PE development, including past PIH or twin pregnancy. Subjects with hypertension, diabetes, chronic renal disease, immunological or vascular disorders, multiple pregnancies, maternal medical disorders related or unrelated to pregnancy, or calcium supplementation were excluded.

History and Examination: The study collected data from patients through a checklist questionnaire, including age, residence, occupations, socioeconomic status, educational levels, family, social, and drug history. Pregnant women provided written consent and underwent a thorough examination, including blood urea, S. creatinine, and S. uric acid. The urinary calcium/creatinine ratio was analyzed, with a cut-off for CCR of ≤ 0.04 [8, 9] .

Statistical Analysis: The study collected data in Microsoft Excel 2010 and used IBM-SPSS 26 for statistical analysis. Frequencies, means, and standard deviations were calculated using t-tests, Chi square tests, and Fissure Exact tests. One-Way ANOVA was used to calculate differences among groups, with a P-value of ≤ 0.05 considered significant.

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Results

This study involved 150 pregnant women divided in to3 groups: 50 PE, 50 PIH, and 50 control. The mean maternal age was higher in the PIH group. Rural residents constituted 80.0%, 56.0%, and 60.0% of the control, PIH, and PE groups, respectively. Enough monthly income was found in 50.0% of control, 44.0% in PIH, and 68.0% in PE. Moreover, the study found that of 48.0% the PE group had nulliparous pregnancies,12.0% had pregnancies with a Para ≥5. No abortion was found in the PE group was significantly higher (0.001) . About half of the control group and more than half of PIH group had gestational age of 37-41^6 weeks, while one third of the PE group was at 37-416. Meanwhile, < 32 weeks gestational age was found in 12.0%, 4.0%, and 18.0% of the studied groups (Control, PIH, PE) respectively. No significant difference was found in the ANC among the studied groups as shown in Table 1.

Table 1: Comparison of Socio-Demographic and Obstetrical Characteristics.

Socio-demographic characteristics		**Control**	**PIH**	**PE**	***p*-value***
		Mean ±SD	Mean ±SD	Mean ±SD	
Maternal Age (years)		25.5±3.8(A)	33.2±8.0(B)	28.1±5.6(A)	**0.000**
		No.(%)	**No.(%)**	**No.(%)**	**p-value****
Residence	Urban	10(20.0)	22(44.0)	20(40.0)	**0.001**
	Rural	40(80.0)	28(56.0)	30(60.0)	
Income/ month	Enough	25(50.0)	22(44.0)	34(68.0)	**0.000**
	Not enough	25(50.0)	28(56.0)	16(32.0)	
Parity	Nulliparous	20(40.0)	12(24.0)	**24(48.0)**	**0.010***
	Para 1	4(8.0)	0(0.0)	4(8.0)	
	Para 2-4	16(32.0)	18(36.0)	16(32.0)	
	Para ≥5	10(20.0)	**20(40.0)**	6(12.0)	
Abortion	Yes	15(30.0)	24(48.0)	7(14.0)	**0.001***
	No	35(70.0)	26(52.0)	**43(86.0)**	
Gestational age (week)	<32	6(12.0)	2(4.0)	9(18.0)	**0.036***
	32-33^6	9(18.0)	10(20.0)	8(16.0)	
	34-36^6	13(26.0)	8(16.0)	18(36.0)	
	37-41^6	22(44.0)	**30(60.0)**	15(30.0)	
ANC	≤3	8(16.0)	8(16.0)	9(18.0)	0.384***
	≥4	41(82.0)	38(76.0)	39(78.0)	
	No	1(2.0)	4(8.0)	2(4.0)	

*One-Way ANOVA with post hoc test; same letters mean no significance while different letters mean significant difference; **Chi square test; *** Freeman-Halton Exact test

Comparison of biochemical investigations among the studied groups were demonstrated in Table 2. The blood urea mean level was significantly differed among the studied groups with the lowest mean among the control group. The serum uric acid mean level among control was significantly lower than among the PIH and PE. The difference of the mean Calcium in urine lower in PE group than those in control and PIH but not significant. Creatinine in urine showed higher in PE group but not significant. Mean level of urinary calcium/creatinine ratio among the control was significantly higher than among the PE only.

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Table 2: Comparison of Biochemical Investigations among the Studied Groups.

Biochemical investigations	Control	PIH	PE	p-value*
	Mean ±SD	Mean ±SD	Mean ±SD	
B. Urea (mg/dl)	15.8±4.5 (A)	19.1±5.6 (B)	24.3±9.4 (C)	**0.000**
S. Creatinine (mg/dl)	1.1±1.8 (A)	0.63±0.17 (B)	0.69±0.2 (AB)	**0.039**
S. Uric acid (mg/dl)	4.4±0.99 (A)	6.1±1.3 (B)	6.6±1.7 (B)	**0.000**
UCa (mg/dl)	8.4±5.3	6.5±5.7	4.3±4.8	0.073
UCr (mg/dl)	115.3±72.1	113.7±63.4	119.4±69.9	0.949
UCa/Cr ratio (mg/mg)	0.11±0.09(A)	0.07±0.06(AB)	0.05±0.1(B)	**0.019**

*One-Way ANOVA with post hoc test; same letters mean no significance while different letters mean significant difference; UCa=Calcium in urine; UCr= Creatinine in urine; UCa/Cr= Urinary Calcium/creatinine ratio

Comparison of biomarkers investigations among the studied groups was demonstrated in Table 3 which elicited that urinary calcium-creatinine ratio, blood urea, S. creatinine, S. AST, and S. ALT among mild PE were lower than that among the severe PE but the associations were statistically not significant. The S. uric acid mean level among the mild was insignificantly higher than that among the severe PE group.

Table 3: Comparison of Biomarkers Investigations among the PE Groups.

Biomarkers Investigations	Severity of PE		p-value*
	Mild Mean± SD (n=21)	Severe Mean± SD (n=29)	
Urinary Calcium-creatinine ratio(mg/mg)	0.046±0.060	0.067±0.114	0.448
Blood Urea (mg/dl)	24.19±10.146	24.50±9.068	0.909
S. Creatinine (mg/dl)	0.607±0.217	0.765±0.210	0.012
S. AST (U/L)	28.76±18.080	48.44±51.617	0.101
S. ALT (U/L)	22.23±15.594	38.96±35.694	0.052
S. Uric acid (mg/dl)	6.80±2.031	6.60±1.588	0.688

*t-test for independent two means

Urinary Calcium/ Creatinine ratio done by ROC test and showed that between control and PE showed poor area under the curve (0.233) with a significant statistical association (*P*=0.000). The most appropriate cut-off point was (0.055) with sensitivity=32.0%, specificity 30.0%, PPV= 31.4%, and NPV= 30.6% while between control and PIH and between the two types of PE, the associations were not significant as shown in Table 4.

Table 4: ROC Test Urinary Calcium/Creatinine Ratio.

Area		Std. Error[a]	p-value.[b]	95% Confidence Interval	
				Lower Bound	Upper Bound
Control vr. PIH	0.398	0.058	0.079	0.284	0.512
Control vr. PE	0.233	0.051	**0.000**	0.133	0.333

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Mild vr. Severe PE	0.514	0.084	0.0867	0.349	0.679

Discussion

Hypertensive disorders during pregnancy are important health issues that need to be addressed, especially in developing countries where the incidence and rates of adverse outcomes are higher [9]. The study found no significant difference in mean maternal age between PE and control groups, with the PIH group having a higher mean maternal age. This finding is consistent with reported by Jindal et al., study [10]. while not consistent with previous studies done in Ethiopia [11], which illustrate that women over 35 had higher risk of PE. Rural residence in the current study was the commonest among the studied groups in relation to urban residence with a statistically significant difference which in parallel to the results reported by a study conducted by Ayele *et al.,* study [12]. Enough monthly income was commonly found among the cases of PE than those with not enough income, while most of the PIH group have no enough income with a statistically significant difference. This result was different from that reported by Choe *et al.,* study [13] and Lindquist *et al.,* study [14] which demonstrated that lower household income was an independent risk factor for developing PE.

Regarding the Obstetrical characteristics, the nulliparous was frequently found among the studied groups with statistically significant difference. This corresponded to Bdolah *et al.,* study [15] and this might be due to the pathogenic role of anti-angiogenic factors in preeclampsia. Other studies [16] showed that there was no significant difference between groups regarding to nulli parity. Concerning the abortion in the present study, significant difference was found among the PE with the higher frequencies was reported no abortion, this finding is in accordance with that of Lao *et al.,* [17]. Difference between gestational age and the current studied groups were statistically significant in which half of the controls and 60.0% of PIH group were reached the 37-41^{6} weeks while one third of the PE was in the 34-36^{6} of gestational age. Similarly, women with preeclampsia in the study conducted by Mayrink *et al.,* [18] have more preterm births at less than 34 weeks of gestation than controls. The Fikadu *et al.,* study [19] showed that women at earlier gestations are at an increased risk of pre-eclampsia. Concerning the association of the ANC among the studied groups in the current study, Adu-bonsaffoh *et al.,* [20] reported that there was no statistically significant difference. In the Ashanti region, Ghana, poor quality of ANC was found to be the main cause for the burden of hypertensive disorders in pregnancy is high affecting over (21.4%). Salma *et al.,* [21] concluded that the no. of the ANC visits was significantly related to pregnancy-induced hypertension.

The biochemical investigations among the studied groups showed that the means levels of blood urea and S. uric acid were significantly higher among the PE than the control with no significant differences were found between the mild and severe PE, meanwhile urinary calcium/ creatinine ratio was significantly lower among the PE in comparison to control with no difference was noted regarding the calcium/creatinine ratio between the two types of PE. Shilpa *et al.,* [22] from Turkey investigated 56 cases and found that urinary calcium/creatinine ratio was significantly lower in the PE group (4.56±1.19 mg/mg) compared with the normotensive group (9.23±3.49 mg/mg; $P < 0.05$). Garima *et al.,* study [23] found a significant relationship between urine calcium and hypertensive disorders during pregnancy, and suggested the urine CCR ratio as a proper screening test for PE. However, according to Babaei *et al.,* study [24], *no significant relationship was found* between urine CCR ratio and hypertensive disorders during pregnancy and other researchers have found similar results [25], it is noteworthy that the lack of a relationship between urine CCR ratio and hypertensive disorders in these study, could be due to the small sample size and low incidence of hypertensive disorders. In Ibrahimi *et al.,* [26] there is a highly significant difference between preeclampsia and normotensive pregnancies regarding serum uric acid and between the types of PE.

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Calcium/creatinine ratio was done by ROC test between control and PIH, between control and PE and between the types of PE and found that the significant association was only between control and PE, in which the most appropriate cut-off point was (0.055), this study were almost close to the study of Dutt and Dev [(27)] were conducted the ROC with the collected data and the cut off point for urine CCR ratio used was 0.0669, Garima et al., study [(23)] on statistical analysis, urine CCR ratio in which the most appropriate cut-off point was ≤0.04, and the ROC was used by Ahirwar study (2021) [(28)] calculated predictive cut-off value of urine CCR ratio and which was calculated (0.04). While, Ibrahimi *et al.,*[(26)] found that the 24-h urine calcium/creatinine ratio, which corresponds to a value of 0.105 (cutoff) which far from these study.

Conclusions:
The urinary calcium/creatinine ratio among the studied groups had lower mean level among the preeclampsia group in relation to control, therefore urinary Calcium/Creatinine ratio might be played a role in predicting preeclampsia and have no role in detection the severity of preeclampsia.

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