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A Comparative Study of High Sensitive C-Reactive Protein (hs-CRP) and Urinary Calcium/Creatinine Ratio in Normal Pregnancy and Pregnancy Induced Hypertension in Gujarat, India

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Authors' contributions

This work was carried out in collaboration between all authors. Author SNV designed the study, performed the statistical analysis. Author AVM wrote the protocol, wrote the first draft of the manuscript. Author SK managed the analyses of the study. Authors JD and HS managed the literature searches. Author KM helped in stastical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Background: Pregnancy-induced hypertension (PIH) is a condition characterized by high blood pressure during pregnancy. It is the most common leading cause of maternal and perinatal morbidity and mortality in females. Serum high sensitive C-reactive protein (hs-CRP) is one of the suitable markers for low grade inflammation evaluation. Urinary calcium-creatinine ratio (UCa/Cr) is a valuable marker for prediction of PIH.

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Aim: To measure & correlate serum hs-CRP and urinary calcium-creatinine ratio in between pregnancy-induced hypertension and normal pregnancy.
Material & Methods: In present study total 150 subjects attending Department of Obstetrics & Gynecology at Sir Takhtsinhji Hospital, Bhavnagar, Gujarat, were included which were categorized in two groups. Group A: 75 patients of pregnancy-induced hypertension; Group B: 75 normal pregnant women as a control group. They were primarily diagnosed based on measurement of blood pressure, clinical examination followed by biochemical investigations like hs-CRP, urinary calcium & creatinine, RBS, urea, creatinine, uric acid, CK-MB. Written informed consent was obtained from all participants before enrolling in the study.
Results: No significant change in the levels of biological parameters like RBS, urea, creatinine and CK-MB was observed in both the study groups ($p>0.05$) except serum uric acid shows a significant difference ($p<0.001$). The levels of hs-CRP were found to be significantly higher in patients of pregnancy-induced hypertension (7.81±3.681)as compared to the normal pregnant women (3.11±1.972)($p<0.0001$) .UCa/Cr ratio had more sensitivity and specificity than hs-CRP for prediction of pregnancy-induced hypertension compared to normal pregnancy.
Conclusion: UCa/Cr ratio can be used as a more sensitive and specific test to detect pregnancy induced hypertension.

Keywords: Hs-CRP; urinary calcium creatinine ratio; pregnancy induced hypertension.

1. INTRODUCTION

Pregnancy induced hypertension (PIH) is one of the most common leading cause of maternal and perinatal morbidity and mortality in females & it complicates approximately one out of every ten pregnancies. Early detection of PIH is more important to save mother and fetal life. PIH is associated with increased risks of serious outcomes such as premature delivery, intra uterine growth retardation (IUGR), perinatal mortality & morbidity, acute renal failure, acute hepatic failure, intra-partum haemorrhage, post-partum haemorrhage, maternal mortality & morbidity following complication such as haemolysis (H), elevated liver enzymes (EL), low platelets (LP) (HELLP syndrome), disseminated intravascular coagulation (DIC) and seizures. [1,2,3,4].

Pre-eclampsia (PE) is most common complication of pregnancy induced hypertension. The incidence of PE in hospital practice varies widely from 5 to 15% in India. The incidence of PE in primigravidae is about 10% and in multigravidae 5%. The etiology of endothelial dysfunction in PE is not known, but it has been postulated to be part of an exaggerated maternal inflammatory response to pregnancy [5,6,7,8].

There has been an increasing interest for the detection of pregnancy disorders before the symptoms actually occur. Endothelial dysfunction is accompanied by elevated levels of inflammatory markers. Indeed, such marker levels have been shown to be much higher in women with PE compared to normal pregnant females [9].

Serum high sensitive C-reactive protein (hs-CRP) is one of the suitable markers for low-grade inflammation evaluation. This marker rises subsequent to stress which are accompanied by endothelial dysfunction and lead to peripheral vascular remodelling, decreased compliance and vascular stiffness. Inflammation is considered to have a crucial role in pathophysiologic mechanism of PE and endothelial dysfunction is accompanied by elevated levels of inflammatory markers [10].

Urinary calcium-creatinine ratio (UCa/Cr) is a valuable marker for prediction of PIH. [11] Physiological changes during normal pregnancy leads to increase in glomerular filtration rate those results in increasing of creatinine clearance and calcium excretion in urine. But in women developing PE because of vasospasm and decrease of renal flow, creatinine clearance decreases, followed by increase in serum creatinine level [12].

Anil bargale et al. concluded that there was significantly increased level of serum hs-CRP in PE patients as compared to normal pregnant women. They also found positive significant correlation between hs-CRP levels and blood pressure [13].

Amandeep Kaur et al. demonstrated that urinary calcium excretion in preeclamptic females was significantly lower than that observed in case of age matched normal pregnant females and

normal non pregnant females which rules out the possibility of decreased resorption of calcium at the level of renal tubules, while urinary creatinine excretion in normal pregnant females was found to be more than that observed in case of normal non-pregnant females, which were responsible for the decreased urinary calcium: urinary creatinine ratio in PE compared to normal pregnancies [5].

Keeping in view the different outcomes of the researchers, pregnancy induced hypertension remains most significant and intriguing unsolved problem in obstetrics. With the background of above facts the present study is designed to determine and correlate the level of serum hs-CRP and UCa/Cr ratio between normal pregnancy and PIH.

1.1 Objectives for the Present Study Were

- To compare serum high sensitive C-reactive protein level, urinary calcium and urinary creatinine level in normal pregnancy and pregnancy induced hypertension.
- To compare random blood sugar, urea, creatinine, uric acid, creatine kinase-MB level in normal pregnancy and pregnancy induced hypertension.
- To study the correlation of high sensitive C-reactive protein, urinary calcium/creatinine ratio in between normal pregnancy and pregnancy induced hypertension.

2. MATERIALS AND METHODS

The present study was conducted at Department of Biochemistry, Government Medical College and Sir Takhtsinhji General Hospital, Bhavnagar in which 75 cases of pregnancy induced hypertension and 75 normal pregnant women with normal blood pressure as a control group were included. Informed consent was taken from them. All cases were admitted to the Gopnath maternity ward (obstetric ward) of Sir T. General Hospital, Bhavnagar. They were primarily diagnosed for pregnancy induced hypertension by clinical examination followed by Biochemical investigations. The subjects in control group were selected by measuring blood pressure and by following inclusion-exclusion criteria.

Case Group - Patients of pregnancy induced hypertension = 75
Control Group - Normal pregnant women = 75

2.1 Inclusion Criteria: (For Cases)

- Pregnant women with gestational age >20 week.
- Patient is a case of hypertension - Pre-eclampsia, eclampsia and gestational hypertension (systolic blood pressure greater than 140 mm Hg or diastolic blood pressure 90 mm Hg)
- Singleton pregnancy

2.2 Exclusion Criteria: (For both Groups)

- Not willing to participate in study
- Rheumatoid arthritis/Cardiovascular disease/Renal disorder/Diabetes mellitus
- Any recent or present fever or infectious disease
- Multiple pregnancy
- Smoking
- Any vaginal bleeding
- Previous history of PIH/Chronic hypertension

2.3 Laboratory Investigations

Venous blood sample was collected in plain and fluoride vacutainer and urine sample was collected in sterile urine container. All the samples were analyzed on fully auto analyzer ILAB-650 (Instrumentation Laboratory, Italy) at NABL accredited Clinical Biochemistry Section, Laboratory Services Sir T. Hospital, Bhavnagar.

Following laboratory investigations were done in study group and control group.

From Venous Blood:

- high sensitive C-reactive protein
- Random blood sugar
- Blood urea
- Serum creatinine
- Uric acid
- Creatine kinase - MB

From Urine Sample:

- Urinary calcium
- Urinary creatinine

For all the investigations, SOPs were used. Estimation of high sensitive c- reactive protein (hs-CRP) was done by turbidimetric immunoassay method [14] urinary calcium by modified arsenaso method [15] creatinine by

Modified Jaffe's Kinetic method [16], RBS by Glucose oxidase peroxidase, urea estimation by urease-gldh kinetic method, uric acid by uricase, CK-MB estimation by immuno-inhibition method [17,18]. Internal quality control and results of external quality control for the above parameters were within range. No test was done from hemolyzed sample, repeat sample was ordered.

Biological reference interval of RBS is upto 140 mg/dl, urea is 15-45 mg/dl, creatinine is 0.6-1.1 mg/dl, uric acid is 2.6-6.0 mg/dl, CKMB is 18-51 U/L and hs CRP is 0.3 – 8.8 mg/l.

Data were analyzed by using GraphPad instat version 3.0. In data analysis, comparison of these parameters were carried out by applying unpaired t-test and Fisher's exact test. Interpretation was done according to p-value. *p < 0.05 - significant and **p < 0.001 - highly significant. All the subjects were divided in following groups:

Group A: Patients of pregnancy induced hypertension (Case group).
Group B: Normal pregnant women who volunteered to participate in the present study. (Control group).

3. RESULTS

The present study included 75 patients of pregnancy induced hypertension and 75 normal pregnant women with normal blood pressure as a control group in which hs-CRP and urinary calcium, urinary creatinine, urinary calcium creatinine ratio were measured.

Mean ± SD of age among cases was 24.65±4.180 years which include 13 patients (17%) ≤ 20 years, 39 patients (52%) between 21-25 years, 17 patients (25%) between 26-30 years and 6 patients (8%) **≥** 31 years of age. The maximum number of patients belongs to age group between 21-25 years. In controls Mean ± SD of age was 24.52±4.078years which include 10 normal pregnant women (13%) ≤ 20 years, 45 normal pregnant women (60%) between 21-25 years, 16 normal pregnant women (21%) between 26-30 years and 4normal pregnant women (5%) **≥** 31 years of age. The maximum number of normal pregnant women belongs to age group between 21-25 years. There was no statistically significant difference of age between two groups.

Table 1 shows the mean level of systolic blood pressure was 153.89±12.512 in Group A and 113.81±7.599 in Group B, while diastolic blood pressure level was 97.14±9.799 in Group A and 73.70±6.768 in Group B. Patients of PIH has significantly higher level of systolic and diastolic blood pressure than normal pregnant women ($p<0.0001$), difference between them were statistically highly significant ($p<0.0001$).

As per Table 2, only serum uric acid shows significant difference ($p<0.001$) in between two groups where as other biochemical parameters like RBS, urea, creatinine and CK-MB did not show significant difference in their values($p>0.05$) in both the groups. As evident from Table 5 mean and SD of serum hs-CRP was 7.81±3.681 in group A and 3.11±1.972 in Group B, difference between them were statistically highly significant ($p<0.0001$). Mean and SD of urinary calcium was 6.95±1.703 in group A and 9.79±3.370 in Group B. Patients of PIH have significantly lower urinary calcium level than normal pregnant women, difference between them were statistically highly significant ($p<0.0001$). While mean and SD of urinary creatinine was157.61±53.159 in Group A and 103.88±40.817 in Group B. Urinary creatinine level was significantly higher in patients of PIH as compared to normal pregnant women, difference between them were statistically highly significant ($p<0.0001$). Moreover, mean and SD of urinary calcium creatinine ratio was 0.047±0.023in group A and 0.105±0.047 in Group B. Patients of PIH have significantly lower UCa/Cr ratio than normal pregnant women, difference between them were statistically highly significant ($p<0.0001$) where, comparison of two groups was done by unpaired t-test.

Table 3 and 4 shows the Sensitivity, Specificity, Positive predictive value & Negative predictive value of serum hs-CRP and urinary calcium creatinine ratio by using Fisher's exact test. As evident from Table 4 at the cutoff level of 5 mg/L for hs-CRP the sensitivity of hs-CRP in relation to pregnancy induced hypertension is 77% and the specificity is 82%. Positive predictive value is 81%, while the negative predictive value is 78%. As evident from Table 4, at the cutoff level of 0.057 the sensitivity of UCa/Cr ratio in relation to pregnancy induced hypertension is 80% and the specificity is 86%. Positive predictive value is 85%, while the negative predictive value is 81%. Hence, UCa/Cr ratio had more sensitivity and specificity than hs-CRP for prediction of pregnancy induced hypertension.

Table 1. Comparison of blood pressure levels between Group A and Group B

Statistics	Systolic BP		Diastolic BP	
	Group A PIH	Group B NPW	Group A PIH	Group B NPW
Mean	153.89	113.81	97.14	73.70
Standard deviation	12.512	7.599	9.799	6.768
Standard error of mean	1.445	0.8775	1.131	0.7815
Significance	p<0.0001		p<0.0001	

PIH- pregnancy induced hypertension, NPW-normal pregnant women

Table 2. Comparison of biochemical parameters between Group A and Group B

Parameter	Biological reference interval	Group A PIH	Group B NPW	Statistical significance
		MEAN ± SD	MEAN ± SD	
RBS	Up to 140 mg/dl	95.96± 16.665	92.65 ± 13.596	t=1.331 p=0.1851
Urea	15-45 mg/dl	20.88 ± 7.876	19.09 ± 6.927	t=1.475 p=0.1423
Creatinine	0.6-1.1 mg/dl	0.71 ± 0.218	0.66 ± 0.146	t=1.967 p=0.0511
UA	2.6-6.0 mg/dl	6.32 ± 1.655	4.66 ± 1.046	t=7.348 p<0.001
CK-MB	18-51 U/L	31.746 ± 8.320	34.49 ± 8.703	t=1.976 p=0.050
Urinary Calcium		6.92 ± 1.70	9.79 ± 3.37	t=8.548 p<0.0001
Urinary Creatinine		157.6 ± 53.1	103.9 ± 40.8	t=11.751 p<0.0001
UCa/Crratio		0.04 ± 0.02	0.10 ± 0.04	t=7.831 p<0.0001

**p < 0.05 - significant, **p< 0.001 - highly significant, #p ≥ 0.05 - not significant*

Table 3. Serum HS-CRP levels and uca/crratio in Group A and Group B

	Group A PIH (N=75)	Group B NPW (N=75)	Total (N=150)
hs-CRP(mg/l)			
≤ 5	58 (39%)	13 (9%)	71 (47%)
> 5	17 (11%)	62 (41%)	79 (53%)
UCa/Cr ratio			
≤0.057	60 (40%)	10 (7%)	70 (47%)
>0.057	15 (10%)	65 (43%)	80 (53%)

Table 4. Overall predictive value of hs-crp and uca/cr ratio in study groups

	HS-CRP	UCA/CR ratio
Sensitivity	77 %	80 %
Specificity	82 %	86 %
Positive predictive value	81 %	85 %
Negative predictive value	78 %	81 %

Table 5. Comparison of HS-CRP levels between Group a and Group b

Statistics	hs-CRP (R.I. = 0.3 – 8.8 mg/l) (n=75)	
	Group A PIH	Group B NPW
Mean	7.81	3.11
Standard deviation	3.681	1.972
Standard error of mean	0.4250	0.2277
Significance	p<0.0001	

4. DISCUSSION

Pregnancy induced hypertension (PIH) is associated with high maternofoetal mortality and morbidity in both underdeveloped and developed countries. Approximately 70% of hypertensive disorders are due to pre-eclampsia (PE).In modern obstetric practice, hypertensive disorders of pregnancy are understood to encompass a clinical spectrum of abnormalities ranging from minimal elevation in blood pressure to severe hypertension with multiorgan dysfunction. The worldwide incidence of PE is 3-4% of all pregnancies [19]. In the United States, PE accounts for 15% to 17.6% of maternal deaths. In India the incidence was reported as 8-10% of pregnancies being 10% in primigravida, 5% in multigravida [2].

While the exact causes of PE are not well understood, certain factors may increase a woman's risk of developing PIH or PE. The current hypothesis regarding the etiology of PE focuses on mal-adaptation of the immune responses and defective trophoblast invasion. Thus, an excessive maternal inflammatory response, perhaps directed against foreign fetal antigens, results in a chain of events including shallow trophoblast invasion, defective spiral artery remodeling, placental infarction and release of pro-inflammatory cytokines in the systemic circulation [2,9].

It has been shown that CRP is elevated in women with PE [20] Determination of hs-CRP has been suggested to be more sensitive than conventional measurement of CRP and provides better sensitivity in confirmation of inflammation. Recently, several studies have conducted to elucidate a relationship between PE and serum hs-CRP levels [21].

Renal excretion of calcium increases during pregnancy, maximum excretion levels reached during the third trimester. Urinary excretion of calcium levels in non-pregnant women is in the range about 100 - 250 mg/day, in pregnant women the range is between 350-620 mg/day. There is a decrease in urinary calcium levels in pre-eclampsia. Decreased renal filtration and increased tubular reabsorption may result in hypocalciuria [22].

The aetiology of hypocalciuria in preeclamptic patients is unknown. It has been speculated that hypocalciuria may result from decreased dietary intake, decreased intestinal absorption, increased calcium uptake by the fetus and placenta, or intrinsic renal tubular dysfunction [23].

The mean and SD of systolic blood pressure was high 153.89±12.512 in patients of PIH and 113.81±7.599 in normal pregnant women, while diastolic blood pressure washigh 97.14±9.799 in patients of PIH and 73.70±6.768 in normal pregnant women with statistically significant difference ($p<0.0001$) (Table 1).

Only serum uric acid shows significant difference ($p<0.001$) in between group A and Group B. The mean and SD of serum hs-CRP was 7.81±3.681 in patients of PIH and 3.11±1.972 in normal pregnant women, difference between them were statistically highly significant ($p<0.0001$).

According to Vijayalakshmi et al.[10]serum hs-CRP level significantly elevated in pre-eclampsia suggesting pre-eclampsia to be an exaggerated inflammatory condition when compared to normal pregnancy.

Yasmin Ashraf et al. [23] reported that serum hs-CRP level measured in preeclamptic group were significantly higher 14.80±0.679 mg/l compared to control group 4.978±0.336 mg/l with p-value 0.0001.

Zaima Ali et al. [24] in 2013 discovered that The hs-CRP level was significantly increased in third trimester in pregnancies complicated by PE as compared to normotensive pregnant women and concluded that exaggerated systemic inflammation is characteristic of PE.

In our study patients of PIH have significantly lower urinary calcium level than normal pregnant women ($p<0.0001$). Urinary creatinine level was significantly higher in patients of PIH as compared to normal pregnant women ($p<0.0001$). The mean and SD of urinary calcium creatinine ratio was 0.047±0.023in group A and 0.105±0.047in Group B. Patients of PIH had significantly lower UCa/Cr ratio than normal pregnant women with statistically significant difference ($p<0.0001$) (Table 2).

N.V. Lakshmi et al. [1] reported that urinary calcium creatinine ratio was used in prediction of pregnancy induced hypertension & there was significant lowering of urinary excretion of calcium in cases who developed PIH. PIH developed more in cases with UCa/Cr < 0.04.

Rashmi Sinha et al. [25] reported that UCa/Cr ratio at 0.04 in spot urine sample being a good test for prediction of pre-eclampsia can be recommended as a screening test in all asymptomatic pregnant women.

Babli Yadav et al. [26] observed in 2014 that significant fall in urine calcium creatinine ratio in PIH study group compared to normal pregnant women.

Swapna V. S et al. [22] reported that Urinary calcium and creatinine level were significantly decreased in gestational hypertensive patients compared to normotensive pregnant women.

The sensitivity and specificity of serum hs-CRP for prediction of pregnancy induced hypertension was 77% and 82% respectively with 81% positive predictive value and 78% negative predictive value (Table-3,4). The sensitivity and specificity of UCa/Cr ratio for prediction pregnancy induced hypertension was 80% and 86% respectively with 85% positive predictive value and 81% negative predictive value (Table 4).

From above findings it is indicated that serum hs-CRP level was significantly increased and UCa/Cr ratio was significantly decreased in pregnancy-induced hypertension compared to normal pregnancy.

UCa/Cr ratio had more sensitivity and specificity than hs-CRP for prediction of pregnancy induced hypertension compared to normal pregnancy (Table 4).

5. CONCLUSION

In the present study, it is concluded that serum hs-CRP level was significantly increased and UCa/Cr ratio was significantly decreased in pregnancy-induced hypertension compared to normal pregnancy. Serum hs-CRP at the cutoff level 5 mg/Lcan be useful in identifying pregnant women at risk for pregnancy induced hypertension. UCa/Cr ratio <0.057 in spot urine sample can be used as a good test for prediction of pregnancy induced hypertension. However, in patients of PIH serum hs-CRP show less predictive value as compared to UCa/Cr ratio, therefore UCa/Cr ratio can be used as a more sensitive and specific test to detect pregnancy induced hypertension which is a non-invasive and inexpensive test.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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