

Serum Uric Acid and Homocysteine as Predictors of Pre-eclampsia

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Abstract

Objective: To estimate the serum homocysteine and uric acid levels in normal and pre-eclamptic patients and to find out any correlation between these parameters and pre-eclampsia

Study design and setting: Cross-sectional study; Dept. of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences (RIMS); Imphal (Manipur), India.

Methods: Data collected from 50 pre-eclamptic pregnant women and 25 normotensive pregnant women admitted in Antenatal ward, Department of Obstetrics and Gynaecology, RIMS Hospital. The blood samples were collected from these patients and analyzed for serum homocysteine and uric acid level.

Results: The serum homocysteine and uric acid levels were found to be significantly higher in preeclamptic cases than in normal controls. Mean \pm SD of uric acid and homocysteine levels were 8.82 ± 1.68 mg% and 10.32 ± 2.52 μ mol/l respectively in the cases compared to 4.06 ± 0.96 mg% and 3.55 ± 1.25 μ mol/l in the controls. A positive correlation was found between the serum uric acid level, homocysteine and blood pressure. Thus the study showed a strong association between increased uric acid, blood pressure and homocysteine levels.

Keywords: Pre-eclampsia; Uric acid; Homocysteine

Introduction

Hypertension is one of the common complications during pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. Pre-eclampsia is a type of hypertensive disorder complicating pregnancy. It is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after the 20th week in a previously normotensive and non-proteinuric patient. Its pathophysiology is poorly understood but currently endothelial dysfunction is most popularly hypothesized to be a central pathophysiological feature of preeclampsia leading to altered vascular reactivity, loss of vascular integrity and activation of the coagulation cascade [1].

Uric acid (UA) is the major end-product of purine metabolism. The cause of hyperuricemia in pre-eclampsia has been attributed to either a decreased excretion or to an increased production of uric acid. Decreased uric acid clearance, reflected by altered tubular function has been documented, while in 1990 Fay proposed an increased breakdown of purines in the placenta as a possible explanation for the overproduction of uric acid [2]. Hyperuricemia is one of the most consistent and earliest detectable changes in pre-eclampsia and has been cited as a better predictor of fetal risk than blood pressure [3,4].

Homocysteine (Hcy), a thiol-containing amino acid, is the demethylated derivative of the essential amino acid methionine and thus an intermediate in the methionine cycle. Elevated homocysteine is a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis and occlusive vascular disorders [5]. The mean homocysteine levels normally decrease with gestation either due to physiological response to the pregnancy, increase in estrogen, hemodilution from increased plasma volume or increased demand for methionine by both the mother and fetus [6]. The homocysteine-mediated vascular changes are similar to those

associated with preeclampsia; therefore, it has been postulated that hyperhomocysteinemia may be associated with this condition [7].

The present study was conducted to estimate the serum homocysteine and uric acid levels in pre-eclamptic indigenous Manipuri women and to find out any correlation between these parameters and the disease.

Materials and Methods

A case control study was conducted to evaluate the level of serum homocysteine in preeclamptic patients (cases) and normal pregnant women (controls) admitted in the antenatal ward in the Department of Obstetrics and Gynaecology. It was done in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal. Patients who were diagnosed as preeclamptics were taken as the cases and normal pregnant women of comparable gestational age as the controls. Fifty pregnant women in the age group 18 to 45 years having blood pressure \geq 140/90 mmHg and proteinuria \geq 300 mg in a 24 hours urine collection after 20 weeks of gestation were recruited as preeclamptic cases. Another 25 normal pregnant women of similar age group and gestational age were also taken as controls. The study group and the control group were matched for age, weight and gestational age. All

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the cases and controls in the study were subjected to detailed history regarding age, parity, height and weight at the time of blood collection. Maternal education, religion, race, socioeconomic status, menstrual history, obstetric history was taken. General physical examinations and systemic examinations with special reference to oedema and blood pressure were carried out. And all the investigations were recorded in the proforma designed for the study. Those patients with preexisting hypertension, cardiovascular or renal diseases diabetes mellitus or chronic diseases and those patients on treatment with anti-folate drugs (antiepileptics, methotrexate) were excluded from the study. Ethical clearance was obtained from the Institutional Ethical Committee, Regional Institute of Medical Sciences, Imphal.

5 ml of venous blood was drawn from anterior cubital vein after an overnight fast. The sample was centrifuged for 10 minutes and analysed for total serum homocysteine and uric acid in the Department of Biochemistry, RIMS. Total serum homocysteine was carried out by Enzyme Linked Immunosorbant Assay (ELISA) method [8] using Axis-homocysteine Enzyme Immunoassay (EIA) kit from Ranbaxy Diagnostic Ltd. India. Serum uric acid was analyzed by Uricase method (enzymatic-colorimetric test) modified by Human Co., Germany [9,10].

Statistical analysis was done using well known statistical formulae like χ^2 - test, independent sample t-test; Pearson correlation coefficient "r" was used.

Results

Table 1 shows the distribution of preeclampsia women and normal pregnant women among the various religious groups. The majority of women in the case group are Hindus (70%) whereas Muslims and Christian comprises of 20% and 10% respectively. In the control group Hindus comprises of 76% whereas Muslims and Christians comprises of 12% each. It is found that no significant difference ($p=0.683$) is observed between them.

Table 2 shows that majority of the women in the case group belong to the lowest socioeconomic group (60%) followed by women belonging to medium (14%) and high economic status (12%) respectively. The pattern is found to exist in both the groups and no significant difference ($p=0.114$) is observed.

Table 3 shows the distribution of controls and cases according to parity. It is seen that maximum number of cases (50%) occur in primiparas (P_{0+0}), 20% belong to P_{1+0} , 20% belong to P_{2+0} and 10% belong to P_3 and above. Insignificant value of $\chi^2=1.130$; $p=0.769$ suggests that parity is matched between the groups.

It is evident from table 4 that maximum number of the cases occurs in the age group of 21-25 years. The women in control group have older age than that of the case group. However the difference is found to be insignificant at 5% probability level.

Table 5 shows that the mean age \pm standard deviation (SD) in years in the case and control group. The difference between the groups is not significant ($p=0.380$) indicating that both the groups are of comparable age.

Table 6 shows the distribution of cases and controls according to mean \pm SD of weight and haemoglobin. It is observed that mean weight of women in the case group (52.46 ± 5.09 Kg) is more compared to that of control group (50.36 ± 3.55 Kg) but the difference is not significant at 5% level of significance. The haemoglobin concentration is more in the controls (11.20 ± 1.27 gm %) compared to cases (10.36 ± 0.82

Religion	Group		Total
	Control group Number (%)	Case group Number (%)	
Hindu	19(76)	35(70)	54
Muslim	3(12)	10(20)	13
Christian	3(12)	5(10)	8
Total	25(100)	50(100)	75

$\chi^2 = 0.761$; df = 2; $p = 0.683$ df: Degree of Freedom

Table 1: Distribution of case and control group according to religion.

* Socio-economic status	Group		Total
	Control group Number (%)	Case group Number (%)	
High	7(28)	6(12)	13
Medium	3(12)	14(28)	17
Low	15(60)	30(60)	45
Total	25(100)	50(100)	75

$\chi^2 = 4.344$; df = 2; $p = 0.114$

* Kuppaswamy socioeconomic status scale (1981)

Table 2: Distribution of case and control group according to socioeconomic status.

* Parity	Group		Total
	Control group Number (%)	Case group Number (%)	
P_{0+0}	15(60)	25(50)	40
P_{1+0}	3(12)	10(20)	13
P_{2+0}	4(16)	10(20)	14
P_3 and above	3(12)	5(10)	8
Total	25(100)	50(100)	75

$\chi^2 = 1.130$; df = 3; $p = 0.769$

Table 3: Distribution of case and control group according to parity.

Age (yr.)	Control group (%)	Case group (%)	Total
Up to 20	1(4%)	6(12%)	7
21 – 25	8(32%)	25(50%)	33
26-30	10(40%)	9(18%)	19
31-35	4(16%)	5(10%)	9
36 and above	2(8%)	5 (10%)	7
Total	25	50	75

$\chi^2 = 6.13$; df = 4; $p = 0.189$

Table 4: Distribution of case and control group according to the age group.

Group	No. of patients	Mean \pm SD (Years)
Control group	25	27.64 \pm 4.76
Case group	50	26.50 \pm 5.50

SD: Standard Deviation $t = 0.883$; df = 73; $p = 0.380$

Table 5: Comparison of mean age \pm SD (years) of case and control groups.

Parameter	Control group		Case group		t-value	df	p-value
	No. cases	Mean \pm SD	No. cases	Mean \pm SD			
Weight(kg)	25	50.36 \pm 3.55	50	52.46 \pm 5.09	1.845	73	0.069
Hb (gm%)	25	11.20 \pm 1.27	50	10.36 \pm 0.82	3.466	73	3.466

SD: Standard Deviation; df: Degree of freedom

Table 6: Comparison of mean \pm SD of weight and haemoglobin between the case & control group.

gm%). This difference is found to be statistically significant ($p=0.001$).

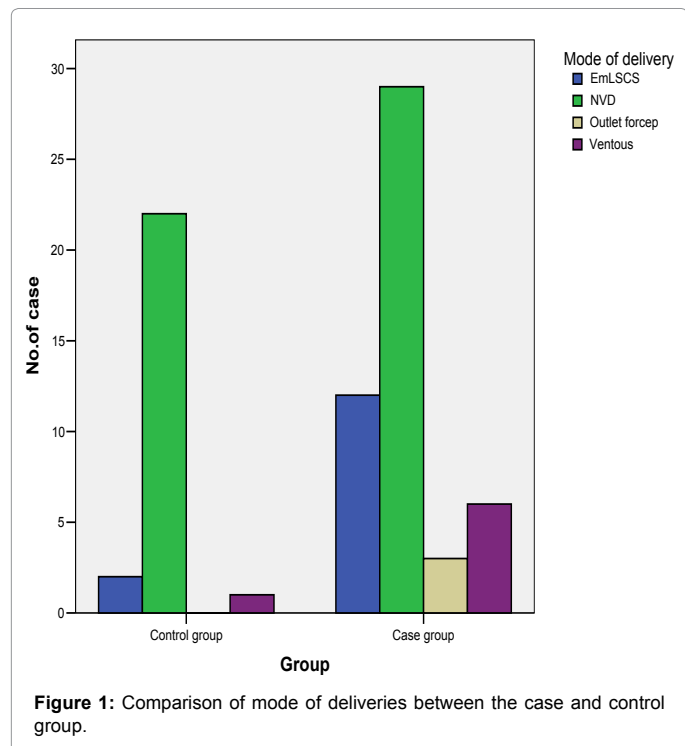
Table 7 shows that majority of the preeclamptic cases (70%) shows the presence of both proteinuria and oedema.

It is evident from figure 1 that regarding the mode of deliveries,

Parameters	Present (%)	Absent (%)	Total
Proteinuria	30(60)	20(40)	50
Oedema	30(60)	20(40)	50
Both	35(70)	15(30)	50

$\chi^2 = 1.44$; df = 2; p = 0.487

Table 7: Proteinuria and oedema in the case group.



maximum number of cases (58%) and controls (88%) delivered by normal vaginal delivery (NVD) followed by caesarean section in 28% and 8% of the cases and controls respectively. Six percent of cases delivered by outlet forceps and the number of patients delivered by assisted ventouse are 12% and 4% in the cases and controls respectively. However insignificant test value ($p=0.068$) suggests that the mode of deliveries in both the groups are almost alike.

Figure 2 shows that the average gestational age at delivery for normal pregnant women (39.00 ± 1.19 weeks) is higher than of the cases (35.94 ± 1.83 weeks). The difference is very highly significant even at 0.1% probability level ($p=0.000$).

The weights of the babies born to normal pregnant controls are more than those born to the cases. Mean \pm SD (Kg) in the control group is 3.11 ± 0.36 compared to 2.80 ± 0.60 in the case group as is evident from figure 3. The difference is statistically significant at 5% probability level ($p=0.023$).

It is evident from table 8 that out of the 50 preeclamptic patients, 88% cases have no complications whilst 8% have intrauterine foetal dead (IUFD), 2% has abruptio placentae and 2% has congenital malformation. In the control group none has complications. The complications that occurred within the case group are found to be highly significant compared to normal pregnant controls ($p<0.001$).

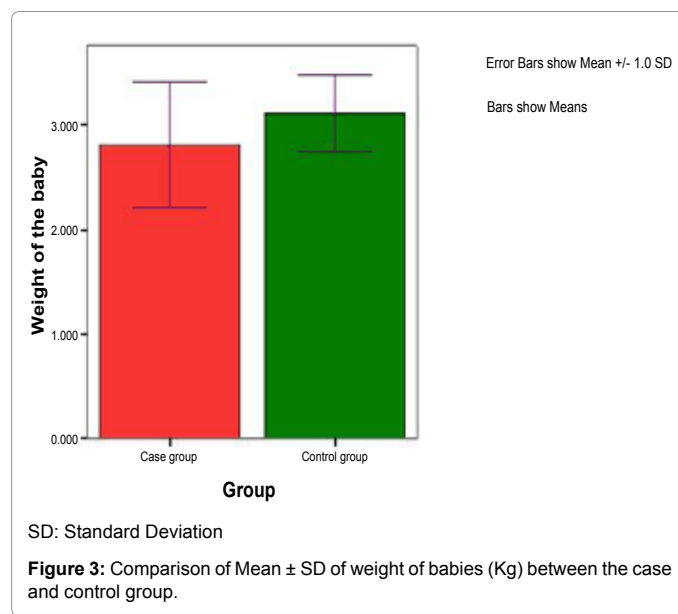
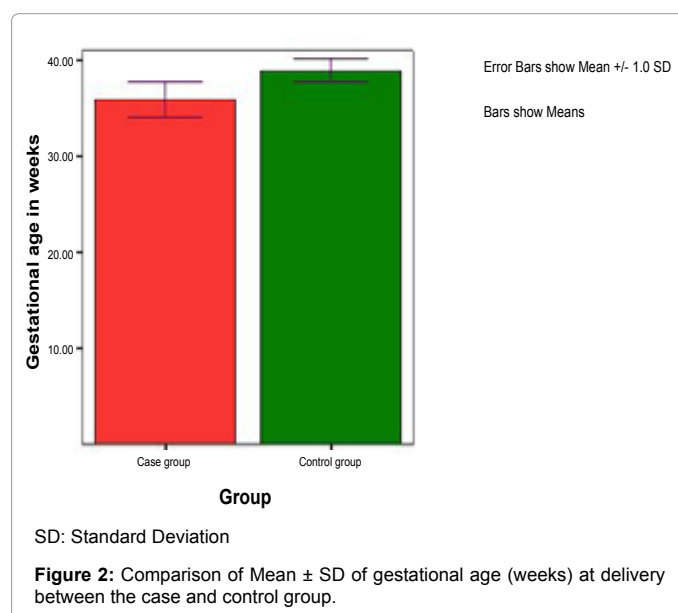
Table 9 shows the comparison of mean \pm SD (mmHg) of blood pressure between the cases and controls. It is seen that the mean \pm SD of systolic as well as diastolic blood pressure level in preeclamptic

women is much higher than that for normal pregnant women. This difference is found to be very highly significant ($p=0.000$).

The serum uric acid levels in the cases are higher than the controls (Figure 1). The mean \pm SD (mg%) for the cases is 8.82 ± 1.68 whereas in the control group it is 4.06 ± 0.96 . This difference in the values is very highly significant ($p \leq 0.001$).

The level of serum homocysteine is higher in the case group compared to control group as evident in figure 2. The mean \pm SD of homocysteine ($\mu\text{mol/l}$) in the case group is 10.32 ± 2.52 whereas the level in control is 3.55 ± 1.25 . This variation is very highly significant as evident by very highly significant value of $t=12.601$ and $p=0.0001$.

Table 10 shows the level of homocysteine levels in preeclamptic (PET) cases according to blood pressure. It has been observed that out of 50 cases of preeclampsia, 30 preeclamptic patients have blood pressure between 140/90 mm Hg and 160/110 mmHg and 20



Complications	Group		Total
	Control group (%)	Case group (%)	
Abruptio placentae	0	1(2)	1
Congenital malformation	0	1(2)	1
Intrauterine fetal death	0	4(8)	4
No complication	25(100)	44(88)	69
Total	25(100)	50(88)	75

$\chi^2 = 106.320$; $df = 3$; $p = 0.001$

Table 8: Distribution of case and control according to complications.

Parameter value	Control group		Case group		t-value	df	p-value
	No. cases	Mean \pm SD	No. cases	Mean \pm SD			
Systolic 0.001	25	118.08 \pm 10.80	50	155.80 \pm 10.65	14.385	73	<
Diastolic 0.0001	25	75.36 \pm 7.73	50	103.16 \pm 15.37	-8.497	73	<

Table 9: Comparison of mean \pm SD of blood pressure (mmHg) level between the case and control group.

Blood Pressure Level(mmHg)	Total No. of Cases	No. of Cases (%) according to Homocysteine Level	
		<10 μ mol/l	> 10 μ mol/l
>140/90 <160/110	30	18(60%)	12(40%)
>160/110	20	7(25%)	13(65%)
Total	50	25	25

$\chi^2 = 2.080$; $df = 1$; $p = 0.148$

Table 10: Homocysteine levels in preeclamptic (PET) cases according to blood pressure.

preeclamptic patients have blood pressure above 160/110 mmHg. In the mild preeclamptic cases majority has homocysteine level below 10 μ mol/l whereas in the severe preeclamptic cases majority of them has level above 10 μ mol/l. But the difference is not significant ($p=0.148$).

In order to study the correlation among the parameters; serum homocysteine, blood pressure, and serum uric acid – Pearson correlation coefficient “r” is advocated and findings are shown in table 11. The analysis is based on the case group only. Table 11 highlights that there is a strong positive correlation between serum homocysteine with blood pressure (systolic and diastolic) which is highly significant. A positive correlation is also observed between serum uric acid and homocysteine.

Discussion

The study shows that majority of the patients are Hindus (70%) followed by Muslims (20%) and Christians (10%) as shown in table 1. This pattern is observed in both the cases and controls and no significant difference ($p=0.683$) is found between them. The reason may be due to the fact that the study is being conducted in the Hindu dominated area.

In the case of socioeconomic status, women in the lowest status (60%) have the highest frequency followed by medium class (28%) and least number of cases belongs to high socioeconomic class (12%) as shown in table 2. The pattern is found to exist in both groups and no significant difference ($p=0.114$) is observed between the groups.

Maximum number of cases is observed in the primigravida (50%) and only 10% of the cases are seen above third gravida (Table 3). Ingec have also reported that preeclampsia occurs more commonly in primiparas compared to normal controls.

In the present study maximum numbers of preeclamptic cases occur in the age group of 21-25 years (59%) and only 10% occurs at 36

years and above (Table 4).The women in the control group are older than women in the case group. However, the difference is found to be insignificant at 5% probability level. Table 5 shows that the mean age \pm SD of the cases is 26.50 ± 5.50 years. This finding is similar to the finding of Powers who found the mean age \pm SD to be 26.2 ± 5.8 years.

On comparison of weight and haemoglobin between the cases and controls (Table 6), it has been observed that the weights of women belonging to the case group are heavier than the controls. Mean weight \pm SD of the cases is 52.46 ± 5.50 kg compared to 50.36 ± 3.55 kg in control but the difference is not statistically significant ($p=0.069$). This finding is in agreement with that of Rajkovic et al. [11] who found in their study that the weights of the preeclamptic women were more than that of the normal pregnant controls.

It is evident from table 7 that maximum cases (70%) show the presence of both proteinuria and oedema whilst proteinuria and oedema alone are seen in 60% each.

The study shows that out of the 50 preeclamptic cases, 44 (88%) cases have no complications, one case (2%) delivered a baby with congenital malformation, one case (2%) has abruptio placenta and another 8% have intrauterine foetal death (Table 8). No complication is seen in the control group. The difference in complication between the cases and controls is highly significant ($p=0.001$).

Our study shows blood pressure is higher in the cases compared to controls and the difference is highly significant as shown in table 9. The serum uric acid level is higher in the cases than the controls (Figure 4) and the difference is highly significant. During pregnancy maternal serum uric acid levels initially falls, with a subsequent rise to prepregnancy levels near term [12]. The third –trimester rise in uric acid may be related to an increase in foetal uric acid production or a decrease in uric acid clearance [13]. Elevated serum uric acid levels due to decreased renal urate excretion are frequently found in women with preeclampsia [14]. Soluble uric acid impairs nitric oxide generation in endothelial cells inducing endothelial dysfunction [15]. Besides the reduced clearance hyperuricemia in pre-eclampsia may be due to increased uric acid production caused by trophoblast breakdown, cytokine release and ischemia. Uric acid can promote endothelial dysfunction, damage and inflammation, which leads to oxidation. So, pre-eclampsia, which is characterized by widespread endothelial dysfunction and inflammation, might be propagated by uric acid [16]. It has also been reported that rise in uric acid level in preeclampsia is secondary to placental damage leading to purine catabolism and production of uric acid. Besides the increased uric acid level in our cases a positive correlation is observed between serum uric acid and homocysteine (Table 11). This supports the finding of Ingec et al. [17].

The serum homocysteine level in the case group is found to be highly significant compared to the control group (Figure 5). The findings are comparable to that reported by Rajkovic et al. [11], Sanchez et al. [18], Harma et al. [19] and Maruotti et al. [20]. A positive correlation is

	Serum Homocysteine	SBP	DBP	Serum uric acid mg%
Serum Homocysteine	1	0.636(*)	0.610(*)	0.029
SBP	0.636(*)	1	0.686(*)	0.032
DBP	0.610(*)	0.686(*)	1	0.007
Serum uric acid mg%	0.029	0.032	0.007	1

* Correlation is significant at the 0.01 level

Table 11: Correlation matrix of serum homocysteine, blood pressure & serum uric acid.

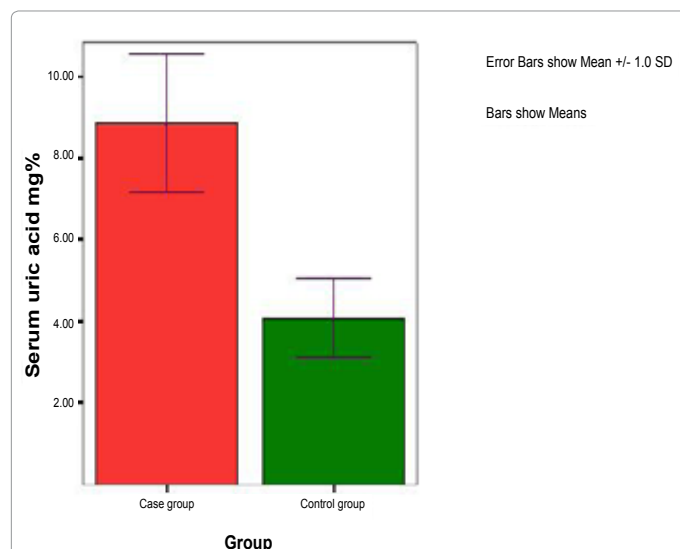


Figure 4: Comparison of mean \pm SD of serum uric acid (mg %) between the case and control group.

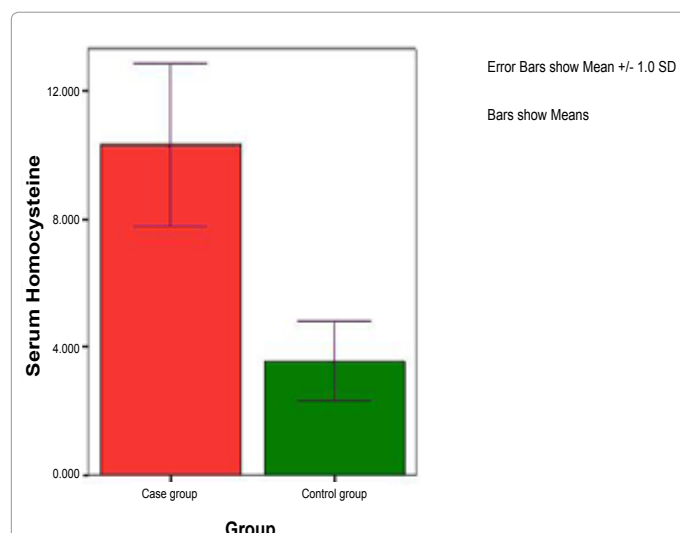


Figure 5: Comparison of mean \pm SD of serum homocysteine (μmol/l) between the case and control group.

seen between serum homocysteine and blood pressure (Table 11). This finding is in agreement with the finding of Ingec et al. [16]. Usually the homocysteine level decreased during pregnancy due to various factors. In the second and third trimesters total plasma homocysteine concentrations in maternal plasma reach only ~50% of those non pregnant women. The decreased level with gestation may be either due to physiological response to the pregnancy, increase in estrogen, hemodilution from increased plasma volume or increased demand for methionine by both the mother and fetus. Studies involving patients with renal disease show an inverse correlation between homocysteine and glomerular filtration rate (GFR) [21]. The GFR increases on an average by 50%-70% above prepregnant levels as early as 5 weeks of gestation and remains elevated throughout pregnancy. However increase in renal function is compromised during preeclampsia [22]. Elevated circulating homocysteine is a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis and occlusive

vascular disorders [23]. It has been suggested that the adverse vascular effects of high homocysteine are mediated by oxidative inactivation of nitric oxide, a powerful endogenous vasodilator released from endothelium [24].

The increased uric acid and homocysteine levels in our cases may be due to derangement in the metabolism that usually decreases their levels during pregnancy. Their increased levels might have led to endothelial dysfunction which eventually results in preeclampsia. The study also shows a strong association between hyperuricemia, hyperhomocysteinemia and preeclampsia.

Conclusion

The results of this study confirm the hypothesis that hyperuricemia and hyperhomocysteinemia are indirect risk factors for preeclampsia. Thus it can be concluded that hyperuricemia and hyperhomocysteinemia can be used as biomarkers for identifying women at risk of complications and adverse pregnancy outcomes.

Several potential limitations of our study are worth mentioning. All the cases were preeclamptic before the measurement of serum uric acid and homocysteine levels and, so it cannot be determined whether the observed elevation in homocysteine and uric acid preceded the development of preeclampsia. Hyperhomocysteinemia and hyperuricemia in preeclampsia patients need to be confirmed in a design in which uric acid and homocysteine are measured before the development of preeclampsia or early in pregnancy in order to identify and monitor the patients at risk and thus provide the best prenatal care for these women and their babies.

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