RESEARCH ARTICLE

Evaluation of Hemoglobin level with Oxidative Stress Markers in the Pregnancy Induced Hypertension and Preeclampsia

Mustafa H. Ghazi,[1] Wurood M. Saleh,[2*] Talib A. H. Mousa[1]

[1]*Department of Chemistry, College of Science, Al-Muthanna University, Samawah, Iraq*
[2]*Department of Gynecology & Obstetrics, College of Medicine, Al-Muthanna University, Samawah, Iraq,*

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ABSTRACT

Objective: The relations between hemoglobin level with serum malondialdehyde, ceruloplasmin, vitamin C, aldosterone, albumin and urine albumin: creatinine ratio in hypertensive complication group of pregnancy.

Design: Case-control study comparing the above parameters in the pregnancy-induced hyper tension, pre-eclamptic patients and healthy control.

Setting: Al Samawa Maternity and Children Teaching Hospital, Samawah, Iraq.

Sample Size: Total 120 women divided into three categories**.** The first category C: 40 healthy women of which 20 women at the 2nd trimester (2C) and the other half at the 3rd trimester (3C). The second category PIH: 40 women with pregnancy-induced hyper tension, 20 of them at 2nd trimester (2PIH) and the other 20 at 3rd trimester (3PIH). The third category PE: includes 40 women with preeclampsia, out of which 20 cases at 2nd (2PE) and the other 20 at the 3rd trimester, (3PE).

Main Outcome Measures: Hemoglobin (Hb)**,** malondialdehyde (MDA), ceruloplasmin (Cp), albumin (Alb), creatinine (Creat), aldosterone (Ald) and vitamin C (Vit C), mean arterial pressure (MAP).

Results: At high MAP of PIH and PE groups, the results revealed positive correlation between Hb level with serum MDA (R= 0.15), Vit. C (R= 0.16). Also found to be weak positive correlation between Hb and serum Cp (R= 0.09), Ald (R= 0.08) and Alb (R= 0.02). However, urine ACR found to be weak negatively correlated (R= -0.05) with the hemoglobin. This study demonstrated that Hb levels have significantly increased in the 2PE (11.68 g/dL) compared with both 2PIH (10.93 g/dL) and 2C (11.08 g/dL) groups. Serum MDA, Cp, and urine ACR levels have significantly increased in PE compared with PIH and C groups at the 2nd trimester (LSD of MDA, Cp, urine ACR = 0.62, 0.70, 3.76 respectively). The same results were found at the 3rd trimesters (LSD= 0.66, 0.71, 5.65, respectively).

Conclusion: At high MAP of PIH and PE groups, a strong positive correlation between Hb level with serum MDA, Vitamin C, also, weak positive correlation between this blood parameter with serum Cp, Ald, and Alb were found. Urine ACR was found to be negatively correlated with Hb. Furthermore, increasing serum MDA, Cp, and urine ACR were detected in PE along with 2nd and 3rd trimesters.

Keywords: Dyslipidemia. Endothelial dysfunction, Endothelin-1, Rosuvastatin.

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INTRODUCTION

Pregnancy-induced hypertension (PIH), defined as hypertension (blood pressure greater than 140/90 mmHg) with or without proteinuria (≥ 300 mg/24 hours), emergent after 20 weeks of pregnancy but resolving up to 12 weeks postpartum[1,2] The occurrence of the disease is 5% to 15% in a general population of pregnant women.[3]

The most lately revised categorization for hypertensive disorder in pregnancy by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2014, as Chronic hypertension, Gestational hypertension, Chronic hypertension with superimposed preeclampsia, preeclampsia, and eclampsia.[4,5] Preeclampsia is determined by the presence of blood pressure ≥140/90 mmHg on two occasions at least 4 hours apart in a woman with previously normal blood pressure and significant proteinuria defined as the excretion of ≥300 mg of protein in a 24 hours urine collection or a protein-to creatinine ratio of at least 0.3 (each measured in mg/dL) in the 3rd trimester.[6]

**Author for Correspondence: mustafachem.93@gmail.com*

Oxidative stress (OS) is produced by a pro-oxidant/antioxidant imbalance, which favors oxidation. In all cells and tissues, lipid peroxidation normally occurs at low levels, but uncontrolled lipid peroxidation may happen in preeclampsia, impairing normal endothelial cell function.[7] Lipid peroxide is extremely reactive and very harmful, caused by tissue damage.[8] Oxidative substances are generally free oxygen radicals and peroxides that routinely form in small amounts.[9] Oxidative stress is generally related with abortive reproductive performance, including infertility, miscarriage, diabetes-related congenital abnormalities, sickle cell anaemia preeclampsia, and sickle cell disease.[10,11] Malondialdehyde (MDA) is one of the most common and reliable markers in clinical situations determining oxidative stress. MDA has been commonly utilized as an appropriate biomarker for lipid peroxidation of omega-3 and omega-6 fatty acids for several years due to its simple reaction with thiobarbituric acid.[12] Antioxidants are molecules that prevent the oxidation caused due to oxidative substances, and they consist of two sub-groups may be enzymatic or nonenzymatic.[13] The enzymatic antioxidants include enzymes like superoxide dismutase, thioredoxin reductase, and glutathione peroxidase. Ceruloplasmin is a blue multi-copper oxidase used as a large carrier of copper ions in the plasma. Cp is an essential component of the cellular defense mechanism against toxicity. It is a single sequence of peptides containing 1046 amino acids that contains a metal-associated protein. Cp's efficiency as an antioxidant is dependent on the quantity of Cu+2 in the protein, as Cp acts to remove the radical O•-2 superoxide by decreasing the copper atom of the protein.[14]

Non-enzymatic antioxidants can be lipid-soluble, like vitamin E, or water-soluble, like vitamin C. Vitamin C is an antioxidant because it prevents the oxidation of other compounds by donating electrons. It also interacts with the tocopheroxyl radical and regenerates reduced tocopherol, acting as a free radical scavenger.[15] Aldosterone is a mineralocorticoid hormone, a type of hormone necessary to live as it regulates the quantities of electrolytes in the body, is secreted by the adrenal cortex, and is responsible for sodium reabsorption into the bloodstream. Aldosterone stimulates potassium excretion. It's the main sodium, potassium, and chloride, metabolism regulator.

Selection of Subjects

This study was conducted at Al Samawa maternity and children teaching hospital in collaboration between maternity and biochemistry departments, from October 2020 to February 2021. Total 120 pregnant women with age range (18–40) years. Forty healthy women with normal, uncomplicated pregnancy, divided to 20 subjects at 2nd trimester (2C) and 20 subjects at 3rd trimester (3C); 40 women with pregnancy-induced hypertension (20 subjects as 2PIH and 20 subjects as 3PIH) and 40 women with preeclampsia (20 subjects for each 2PE and 3PE).

Inclusion and Exclusion Criteria

Clinically diagnosed hypertensive mothers with a gestational age of >14 weeks with an age range 18–40 years. Normal pregnant women of the same gestational age and preeclampsia women were included, while women with twin pregnancies, cardiovascular disease, chronic hypertension, renal diseases, liver diseases, severe anemia and diabetes were excluded from the study.

Collection of Blood Samples

Blood samples are collected. About 5 mL of blood samples of pregnant women with hypertension, preeclampsia, and healthy controls are taken and allowed to clot at room temperature in empty disposable tubes and centrifuged to separate it at 3000 rpm for 10 minutes. The serum samples are separated and kept at -20ºC for later measurement of biochemical parameters unless utilized immediately.

METHODS

Malondialdehyde level, considered a lipid peroxidation marker, was measured using the Fong method.[16] MDA concentrations were calculated, utilizing the molar extinction coefficient of MDA (ƐMDA) equal to 1.56 x 105 $mol^{-1}.Cm^{-1}$. MDA formed from the breakdown of polyunsaturated fatty acid act as a convenient index of peroxidation reaction. Serum Cp levels were determined by Menden method,[17] It is based on Cp-catalyzed oxidation of colorless paraphenylenediamine (PPD) to oxidize blue-violet. There are various techniques for determining albumin concentration. The simplest method is bromocresol green (BCG). The assessment principle is based on BCG's relatively strong affinity to Alb. Albumin in a slightly acidic presence of BCG causes a color change from yellow-green to green-blue.[18] Urinary creatinine concentration was determined according to the kinetic colorimetric assay based on the Jaffé method. In an alkaline solution, creatinine forms a yellow-red complex with picrate.[19,20] Solid-phase, sandwich-format, an immunometric assay was used to determine urinary albumin concentration. The color intensity that depends on Alb concentration is measured quantitatively using the color densitometer NycoCard® READER II. Serum aldosterone and Vitamin

C concentrations were determined by kits of an Enzyme-linked immunosorbent assay (ELISA) (Bioassay technology Laboratory, China).

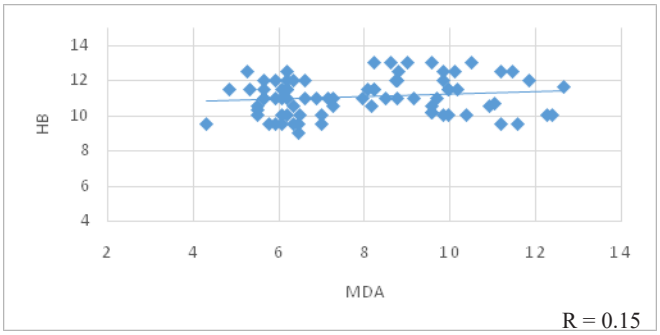


Figure 1: Correlation between Hb and MDA levels of pregnant patient groups at the 2nd and 3rd trimesters

Statistical Analysis

The statistical analysis in this study was performed using Microsoft Excel 2010, and the results are expressed as mean standard deviations (mean SD) with the LSD test. ANOVA-test is used for comparing parameters in various groups studied. Pearson's correlation was utilized to determine the correlation between the current study parameters. *P-values* ($p \leq 0.05$) are considered statistically significant.

RESULTS

The present study revealed a positive correlation between Hb levels with serum concentrations of MDA (R = 0.15), Vit. C (R = 0.16) and with MAP (R = 0.28) along with 2nd and 3rd trimesters (Figures 1–3 respectively). Our results demonstrated that there is weak positive correlation between Hb levels with serum concentrations of Cp (R = 0.09), Ald

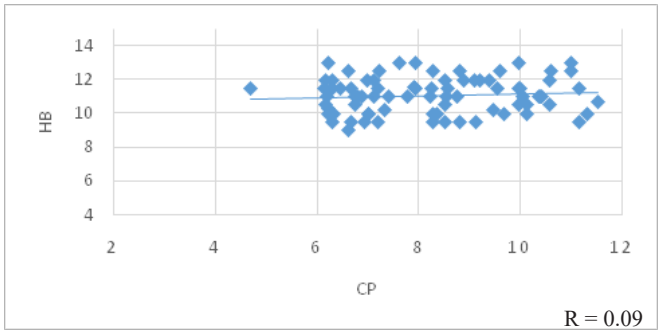


Figure 2: Correlation between Hb and cereluplasmin levels of pregnant patient groups at the 2nd and 3rd trimesters

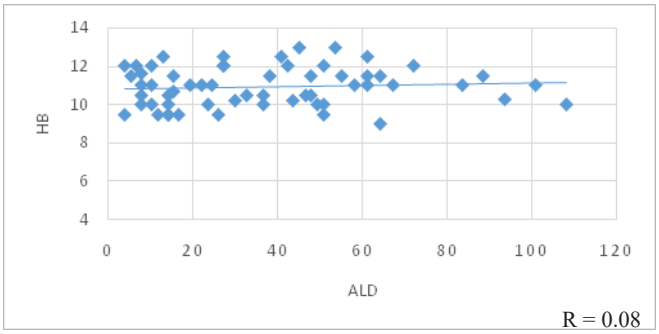


Figure 3: Correlation between Hb and serum aldosterone levels of pregnant patient groups at the 2nd and 3rd trimesters

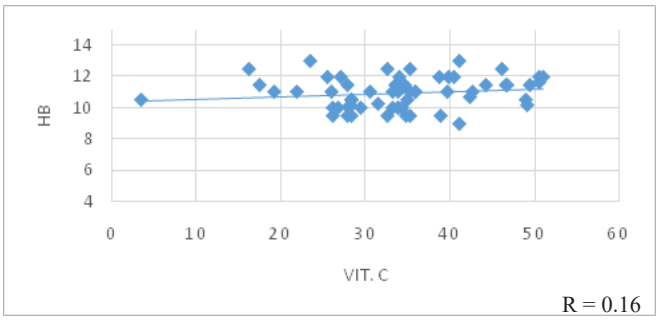
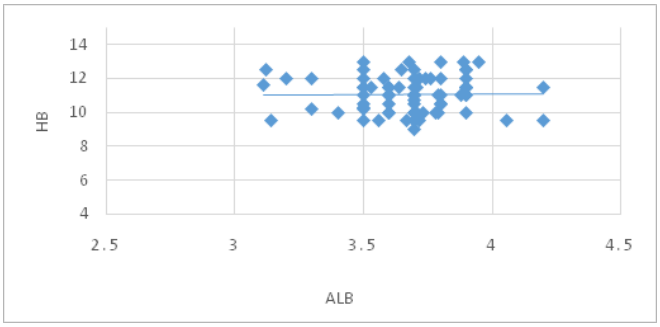


Figure 4: Correlation between Hb and serum Vit. C levels of pregnant patient groups at the 2nd and 3rd trimesters



R = 0.16

Figure 5: Correlation between Hb and serum albumin levels of pregnantpatient groups at the 2nd and 3rd trimesters

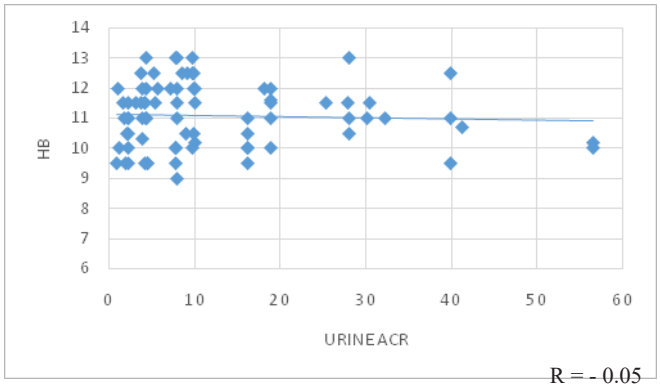
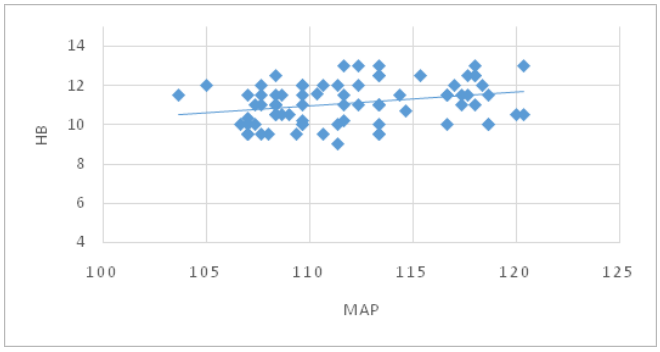


Figure 6: Correlation between Hb and urine ACR levels of pregnant patient groups at the 2nd and 3rd trimesters



R = 0.28

Figure 7: Correlation between Hb and MAP levels of pregnant patient groups at the 2nd and 3rd trimesters

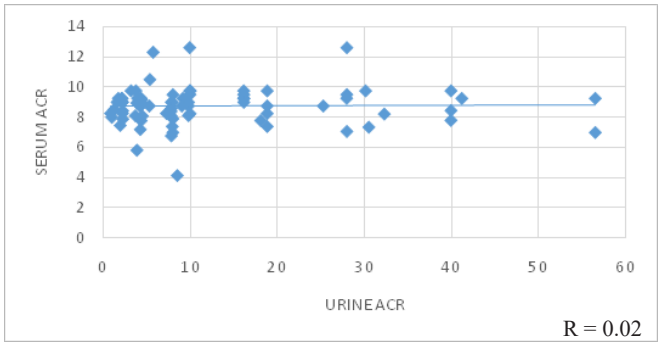


Figure 8: Correlation between serum ACR and urine ACR levels of pregnant patient groups at the 2nd and 3rd trimester

Table 2: Blood and Biochemical parameters of pregnant groups at the 2nd and 3rd trimesters

	2nd trimester				3rd trimester			
	Mean ± SD			LSD	Mean ± SD			
Group	C	PIH	PE		C	PIH	PE	LSD
Hb (g/dL)	11.08 ± 1.00[b]	10.93 ± 1.05[b]	11.68 ± 0.83[a]	0.59	11.13 ± 1.00[a]	10.89 ± 1.11[a]	10.83 ± 1.00[a]	0.66
MDA (µmole/L)	1.85 ± 0.46c	5.82 ± 0.56[b]	9.18 ± 1.54a	0.62	2.18 ± 0.60c	6.67 ± 0.99[b]	10.16 ± 1.37[a]	0.66
Cp (g/L)	2.48 ± 0.69c	7.14 ± 1.11[b]	9.18 ± 1.40[a]	0.70	3.16 ± 0.99c	7.13 ± 0.94[b]	9.58 ± 1.36[a]	0.71
Ald (ng/L)	41.57 ± 34.48[a]	33.04 ± 23.61[a]	39.38 ± 18.36[a]	19.42	48.65 ± 41.83[a]	52.17 ± 34.66[a]	37.29 ± 58.12[a]	33.85
Vit. C (ng/mL)	36.12 ± 13.07[a]	35.61 ± 8.14[a]	30.94 ± 12.41[a]	8.52	34.42 ± 11.03[a]	34.99 ± 7.77[a]	34.49 ± 8.70[a]	7.04
Serum Alb (g/dL)	2.39 ± 0.20[b]	3.60 ± 0.18[a]	3.7 ± 0.20[a]	0.12	2.53 ± 0.22[b]	3.76 ± 3.76[a]	3.66 ± 0.24[a]	0.14
Urine ACR (mg/mmole)	2.59 ± 1.81[c]	3.02 ± 1.38[b]	17.55 ± 10.03[a]	3.76	3.11 ± 2.22[b]	5.38 ± 2.22[b]	24.29 ± 15.14[a]	5.65
Serum ACR (g/mg)	5.94 ± 0.94[c]	8.56 ± 0.69[b]	9.00 ± 1.55[a]	0.12	6.07 ±1.01[c]	8.77 ± 1.32[a]	8.33 ± 1.96[b]	0.14
MAP	88.6 ± 5.24[c]	108.9 ± 2.96[b]	113 ± 3.42[a]	2.53	91.72 ± 4.61[b]	111.4 ± 4.49[a]	114.1 ± 4.12[a]	2.79

Each value represents mean ± SD values with non-identical superscript (a, b or c … etc.) were considered significantly different ($p \leq 0.05$).

(R = 0.08), Alb (R = 0.09) (Figures 4 to 6 respectively). Conversely, it revealed a weak negative correlation between Hb and urine ACR levels (R = -0.05) (Figure 7). The results clarified a weak positive correlation between urine ACR and serum ACR at the period along with 2nd and 3rd trimesters (Figure 8).

Our results demonstrated that Hb levels have significantly increased ($p \leq 0.05$) in 2PE (11.68 ± 0.83 g/dL) compared with each 2PIH (10.93 ± 1.05 g/dL) and 2C (11.08 ± 1.00 g/dL). Hb levels showed nonsignificant difference among all these groups at the 3rd trimester. Serum MDA implied significantly increased in 2PE (9.18 ± 1.54 µmole/L) compared with 2PIH (5.82 ± 0.56 µmole/L) and 2C (1.85 ± 46 µmole/L), also in 3PE (10.16 ± 1.37 µmole/L) compared with 3PIH (6.67 ± 0.99 µmole/L) and 3C (2.18±0.60 µmole/L). Thus, same results were found with respect to Cp (9.18 ± 1.40; 7.14 ± 1.11; 2.48 ± 0.69 g/L) for 2PE, 2PIH, 2C, respectively, and (9.58 ± 1.36; 7.13 ± 0.94; 3.16 ± 0.99 g/L) for 3PE, 3PIH, 3C respectively. Contrarily, Ald and Vit. C concentrations revealed nonsignificant differences at each trimester. Notably, our results have implied that Alb level in 2PE (3.7 ± 0.20 g/dL) doesn't significantly differed compared with 2PIH (3.60 ± 0.18 g/dL), whereas these two values have significantly increased comparing with 2C (2.39 ± 0.20 g/dL). Thus, same results were noticed in 3PE (3.66 ± 0.24 g/dL), 3PIH (3.76 ± 3.76 g/dL) compared with 3C (2.53 ± 0.22 g/dL). The results indicated that urine ACR levels have significantly increased in 2PE (17.55 ± 10.03 mg/mmole) compared with each 2PIH (3.02 ± 1.38 mg/mmole) and 2C (2.59 ± 1.81 mg/mmole). Same results were also found in 3PE (24.29 ± 15.14 mg/mmole), 3PIH (5.38 ± 2.22 mg/mmole) and 3C (3.11 ± 2.22 mg/mmole). However, the values of this parameter have nonsignificant differences in PIH compared with C groups at each trimester. On the other hand, our results found that serum ACR level has significantly increased in 2PE (9.00 ± 1.55 g/mg) compared with 2PIH (8.56 ± 0.69 g/mg) and 2C (5.94 ± 0.94 g/mg). Conversely, the results of the same parameter in the 3rd trimester demonstrated that 3PE (8.33 ± 1.96 g/mg) has significantly decreased compared to 3PIH (8.77 ± 1.32 g/mg). Finally, MAP levels indicated that 2PE (113 ± 3.42) has significantly higher than 2PIH (108.9 ± 2.96) and 2C (88.6 ± 5.24), contrary to the 3rd trimester, where 3PE (114.1 ± 4.12) has non-significantly differed with 3PIH (111.4 ± 4.49). But these two groups are have significantly increased in term of this parameter comparing with 3C (91.72 ± 4.61) (Table 2).

DISCUSSION

Pregnancy is a unique physiological process including complex interplay of inflammatory and anti-inflammatory milieu, hormonal alterations and molecular and cellular events at the maternal-fetal interface.[21] Patra *et al*. concluded that low hemoglobin levels in early gestation are related to preeclampsia and eclampsia and concluded that low periods between pregnancies and low nutritional supports lead to low hemoglobin levels and adverse complications of pregnancy. Particularly in multiparous women.[22] Steer *et al*. also showed that the hemoglobin levels above 12 g/dL at the late second trimester were associated with three times rise in the risk of preeclampsia.[23] Gus Dekker *et al*. proposed that serial measurements of hemoglobin and hematocrit were utilized to monitoring pregnancies at elevated risk of uteroplacental insufficiency. A significant increase in hemoglobin concentrations during in the second trimester may predict the development of pregnancy-induced hypertensive disorders.[24] Blood volume does not rise in women with hypertensive disorders of pregnancy, especially those with preeclampsia, result in relatively elevated hemoglobin concentration.[25]

Our result agrees with some previous researches[26] demonstrated a significant increase in mean value of Hb in group pregnant women with preeclampsia compared to group healthy pregnant women, especially at the 2nd trimester. It is interesting to highlight that Hb level in 2PE gives significant increased value. This behavior has not been see comparing with Hb level at 3PE and other categories. This may give a warning marker or a predictor for early PE, especially if Hb's early trimester was lower.

In addition to that, our results have agreed with others studies reported significantly higher MDA levels in PE

women than in hypertensive and normotensive pregnancy and were significantly higher in hypertensive than normotensive pregnancy.[27,28]

Bernardi *et al*.[29] concluded that pregnancy-induced hypertension (PIH) is a state of extreme raise of oxidative stress and lipid peroxidation.[30] Ceruloplasmin has also ferroxidase action, and its ferroxidatic activity is a crucial function of this enzyme because even trace amount of iron might produce hydroxyl radicals through the fenton reaction which can destroy cellular architecture. Ferroxidatic activity is known to convert toxic ferrous iron to less toxic ferric iron, which decreases oxidative damage to lipids, proteins, and DNA.[31] Our study showed that Cp levels significantly increased in PE compared with H and significantly increased in H compared with healthy groups at each 2nd and 3rd trimester. This finding is consistent with the study of Shamsi AZ who reported that serum level of Cp significantly lower in normal pregnancy than mild and severe preeclampsia.[32]

Shojaati *et al*. pointed The decreased circulating volume circumscribes placental blood supply, finally inducing increased blood pressure through preeclampsia compared to normal pregnancies, proves that pre-eclamptic women have much lower circulating levels Ald.[33] However, our results showed Ald level is low as well but statistically nonsignificant.

Several studies have demonstrated decreased serum levels of vitamin C in preeclamptic patients.[34] Reduced ascorbic acid form is quite effective in protecting plasma lipids and susceptible molecules from peroxidation. Low ascorbate concentration in PE and H relative to normal pregnancy is noticed as well in this study, mainly in the 2nd trimester, but statistically nonsignificant.

This study found that serum albumin level is significantly higher in PE and H groups than healthy controls in the 2nd and 3rd trimester. This agrees with another study[35,] which states that the mean serum albumin levels were significantly higher in preeclampsia.

Our results indicated that urine ACR levels have significantly increased in PE compared with H and C groups. This result does agree with previous researches[36,37,] which demonstrates similar findings. Urine ACR in our results is significantly increased in preeclampsia compared with pregnancy-induced hypertension and healthy control.

Our observations showed that serum ACR is significantly higher in 3PIH than in 3PE. Thus, we can say that serum ACR is not as much affected in PE as urine ACR. We can see that clearly from Table 1. This may indicate the early and the severity of renal damage in PE.

There was a systematic rise of blood pressure in the PIH group until delivery, then it normalizes and near fall but the rises steadily within the first week after birth. Hemodynamic alterations during normal pregnancy involve a decrease in systolic, diastolic and mean blood pressure in the second trimester followed by a slight rise in the third, a decrease in total vascular resistance, particularly in the second trimester, and an increase of cardiac output.[38] Our results agree with previous study[39] which found the MAP in the women with preeclampsia was clearly higher than in the women with normal pregnancy.

A correlation between Hb and MDA level revealed that PIH patients had a higher MDA level than normotensive women. Pandey *et al*. found a concomitant decrease in hemoglobin in response to oxidative stress. Thus, higher levels of the lipid peroxidation product MDA and lower levels of Hb and antioxidants indicate oxidative stress in PIH.[40]

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