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Original Article

Evaluation of Changes in Renal Function of Pregnant Women with Preeclampsia in Al-Jabal Al-Akhdar

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ABSTRACT

Preeclampsia is a multifactorial condition characterized by a constellation of signs and symptoms, including the new onset of hypertension and proteinuria during the last trimester of pregnancy. Women with preeclampsia diagnoses have an increased risk of developing renal diseases later in life. This study was aimed at evaluating serum uric acid, serum creatinine and serum urea in preeclamptic women and comparing values to normal pregnancy women. A total of 100 pregnant women were enrolled in this study. Out of 40 normal pregnant women, 60 suffered from preeclampsia. Blood samples were collected in a plane test tube for the assay of urea, creatinine and uric acid levels. Levels of serum urea and uric acid were increased significantly in the preeclampsia group (29.6 ± 13.8 & 5.80 ± 1.13) compared to the control group (20.50 ± 2.70& 2.982 ± 0.672) respectively. Meanwhile, the level of serum creatinine was increased without any significant differences between the preeclampsia group (0.842 ± 0.346) and the control group (0.798 ± 0.312). Results found a positive association ($p<0.000$) between serum creatinine and serum urea. We conclude from this study that preeclampsia has deleterious effects on renal function as shown by alteration of (serum urea and serum uric acid). These parameters can be taken as predictors of the disease. Therefore, assessment of these parameters helps in monitoring the function of the kidney in preeclampsia.

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INTRODUCTION

Preeclampsia is a multifactorial syndrome marked by a slew of signs and symptoms, including the advent of new-onset hypertension and proteinuria during the third trimester of pregnancy, which is generally accompanied by edema and hyperuricemia. or high blood pressure [1,2,3], or high blood pressure is linked to considerable organic dysfunction after 20 weeks of pregnancy, as well as a high maternal mortality rate due to complications like eclampsia, HELLP syndrome, and edema [4-7]. It causes complications in 2% to 8% of pregnancies, and it is responsible for up to 14% of maternal deaths. patients with severe illness are more likely to have severe consequences, such as Acute Kidney Injury (AKI), according to [8,9]. Though studies have mentioned various parameters in the etiopathogenesis of hypertensive disorders of pregnancy, still it remains obscure [10]. It is originated in the placenta, starting with inadequate cytotrophoblast invasion of the spiral arteries, leading to maladaptation of maternal spiral arterioles, which may be associated with increased vascular resistance of the uterine artery and a decreased perfusion of the placenta [1,11,12]. The only cure is for the affected mother to give birth [11]. It has been observed that preeclampsia has deleterious effects on maternal and perinatal health, particularly in the developing nations of the world [13,14]. While most studies have been undertaken in high-income settings, some inconsistencies exist especially in developing settings where preeclampsia risk factors have been less explored [14,15]. It occurs only in the presence of the placenta, even when there is no fetus (as in hydatidiform mole) and remits dramatically postpartum [3,16]. Preeclampsia (PE) is defined by the development of gestational hypertension (resting systolic blood pressure (BP) 140 and/or diastolic blood pressure (BP) 90 mmHg) at or after 20 weeks of pregnancy in previously normotensive women, according to the international society for the study of hypertension in

pregnancy because proteinuria is only present in 75% of patients, the American College of Obstetrics and Gynecology modified PE recommendations in 2019 specified that "either proteinuria (>300 mg/L per 24-hour urine) or other maternal organ dysfunction" should be present [4,7]. Preeclampsia can also be aggravated by liver and renal dysfunction to varying degrees [17,18]. Pregnant women with preeclampsia or eclampsia have been linked to an increased risk of developing end-stage kidney disease and high blood pressure later in life [14,19,20]. In women with chronic kidney disease (CKD), preeclampsia can occur in up to 40% of pregnancies [14,21]. Laboratory measures include liver function tests, urine protein quantification, and serum creatinine can assist characterize the extent of end organ damage, however none of these are specific for preeclampsia [14]. Pregnancy is connected with alterations in the hormonal, hematological, cardiovascular, and renal systems, despite being a typical physiological phenomenon in women. The alterations in the kidney are linked to a rise in renal blood flow, which leads to a higher glomerular filtration rate [22,23]. That hyperfiltration is caused mostly by a decrease in oncotic pressure. As a result, the renal clearance of creatinine, urea, and uric acid increases. During pregnancy, changes in renal function, as well as alterations in maternal protein and nitrogen metabolism, occur. That all of the above factors result in reduced serum Creatinine, urea, and uric acid levels [24-29]. In a pregnant woman, a normal serum creatinine level can really indicate substantial renal insufficiency [30]. However, when develops preeclampsia, the entire scenario changes [29]. Glomerular Filtration Rate (GFR) and renal plasma flow both decline by 30% to 40% in preeclampsia compared to a normal pregnancy of the same period [3]. Preeclampsia causes a decrease in GFR, which is accompanied by typical histological alterations in the kidney called glomerular endotheliosis, which is marked by fibrin deposition, endothelial enlargement, and capillary space loss space [23,31]. Damage to the glomerular basement membrane and hypoperfusion of the glomeruli, resulting in proteinuria and a reduced glomerular filtration rate. Adaptations to these changes in the kidneys can lead to an increase in blood pressure (BP) [32,33]. Despite a large fall in GFR from the high level during normal pregnancy, blood urea nitrogen (BUN) and creatinine often remain in the normal range for nonpregnant women with preeclampsia [3]. Estimating serum electrolytes, urea, and creatinine can help you comprehend the physiological and pathological changes that occur in preeclampsia. Uric acid in the blood is not only a measure of disease severity, but it also contributes to the pathology of the disorder [10,34]. Preeclampsia is associated with a considerable increase in blood urea and creatinine, according to studies [33,35].Studies on the function of serum uric acid (SUA), urea (SU), and creatinine (SCr) in the pathogenesis of pregnancy-induced hypertension, such as preeclampsia have sparked a lot of interest over the years There are a number of relevant studies available that describe the dependence of these parameter levels in pre-eclamptic and normotensive groups in a confusing and often contradictory manner [35]. This study was planned to evaluate the values of serum uric acid, urea and creatinine in preeclamptic and compared with normal pregnant females.

METHODS

Study design and setting

The present study was conducted in the Dept. of Zoology in Collaboration with Dept. of Obstetrics and Gynaecology Department of the Teaching Governmental Hospital of El- Beida city in Northeast Libya. the study lasted for 12 months from February 2019 to January 2020.Total 100 subjects were selected for study, age ranging from 17 to 45 years. Out of 40 were normal pregnant women, 60 were suffered from preeclampsia. the venous blood was collected from the antecubital vein of each participant without stasis and dispensed into a plastic vacuum plain bottle. Additionally, the blood in the plain bottle was allowed to clot and then centrifuged at a speed of 3000 rpm for 10 minutes. A random venous blood sample (5ml) was drawn from the subjects in to a sterile disposable syringe which was transferred into centrifuge tubes and allowed to clot for 30 minutes. The sample was centrifuged at 3000 rpm for 10 minutes and serum was separated and stored at-20°C until analyzed.

Data collection procedure

Serum UA concentration was measured by an enzymatic colorimetric method [36], [using kits provided by Analyticon ® Biotechnologies AGAmMühlenberg ,Lichtenfels / Germany. The most commonly used techniques for UA determinations are based on the reduction ofphosphotungestate by UA in alkaline medium [37]. Creatinine was determined using ready to use kit from Archem Diagnostics industry. Creatinine reacts with picric acid in alkaline environment to form a color complex. The red color developed is measured photometrically at 500-520 nm. The method in brief is as follows: 100 ul of the sample were mixed with 800 ul of reagent 1 (120 mmol/L carbonate buffer and 360 mmol/L sodium hydroxide) and 200 ul of reagent 2 (7.8 mmol picric acid) and aspirated immediately to photometer (Newman and Price, 1999).

Urea + H2O in the presence of the enzyme urease gives 2 NH3 + CO2. Ammonium ions in the presence of sodium salicylate and sodium hypochlorite form a green color (dicarboxylindophenol). The intensity the color is proportional to the concentration of urea. The absorbance is measured photometrically at 590 nm. The amount of urea is measured using a ready to use kit (Biomaghreb .(10 µl of the sample were mixed well with 800 µl of reagent 1 (2 mmol/l EDTA, 60 mmol/l sodium salicylate, 32 mmol/l sodium nitroprussiate, 30000 U/L urease, and 60 mmol/l phosphate pH 6.7) and 200 µl of reagent 2 (40 mmol/l sodium hypochlorite and 150 mmol/l sodium hydroxide). The samples were aspirated immediately and read photometrically (Archibald, 1945). Recorded data were analyzed using Minitab version 17. Quantitative data were expressed as mean ± SD. The statistics done were: descriptive statistics, person's correlations and independent samples t-test. Probability values $p < 0.05$ were considered statistically significant.

RESULTS

Table (1) shows that the levels of serum urea and uric acid increased significantly in the preeclampsia group (29.6±13.8), and (5.80±1.13) respectively compared to the control group (20.50 ± 2.70), (2.982 ± 0.672). Meanwhile, level of creatinine was increased (0.842 ± 0.346) without statistically significant differences comparison to control group (0.798 ± 0.312). The level of association of the parameters among preeclamptic group studied was evaluated (Table 2). There is no correlation between level of (creatinine and uric acid), and between (uric acid and urea). Serum Creatinine was observed to correlate positively with serum urea ($p<0.000$). In this study, it was used the box chart, which is a convenient way of visually displaying the data distribution through their quartiles. The lines extending parallel from the boxes are known as the "whiskers", which are used to indicate variability outside the upper and lower quartiles. Outliers are sometimes plotted as individual dots that are in-line with whiskers as shown in Figures 1-3.

Table 1. Shows the level of serum urea, serum creatinine and serum uric acid in control and Pre-eclampsia group

Characteristics	Groups	Mean Value	Standard Deviation	P Value
serum urea mg/dl	**Control**	20.50	2.70	0.000
	Pre-eclampsia	29.6	13.8	
Serum Creatinine mg/dl	**Control**	0.798	0.312	0.508
	Pre-eclampsia	0.842	0.346	
Serum Uric Acid mg/dl	**Control**	2.982	0.672	0.000
	Pre-eclampsia	5.80	1.13	

Table 2. Pearson's Correlation Analysis

Variable	Correlation coefficient "r"	P- value
Serum Creatinine vs Serum Uric Acid	0.230	0.078
Serum Creatinine vs Serum urea	0.679	0.000*
Serum urea vs Serum Uric Acid	0.183	0.163

**Correlation is significant at the P < 0.05 level.*

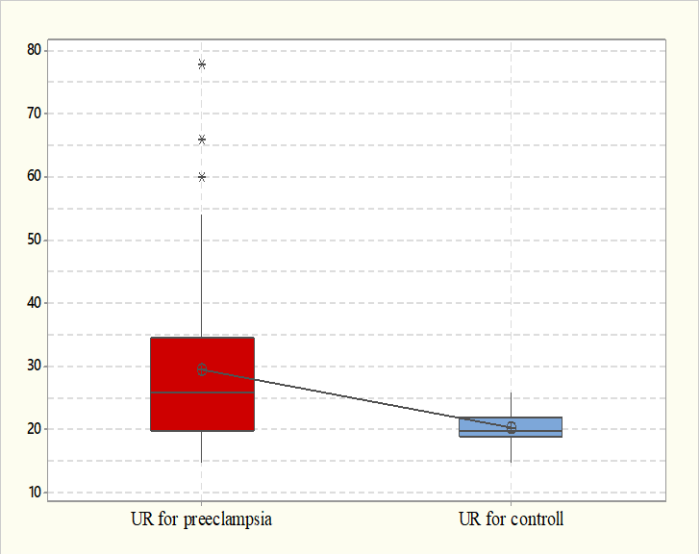

Figure 1: Boxplot for Blood Urea between pre-eclampsia and control groups.

UR: Urea

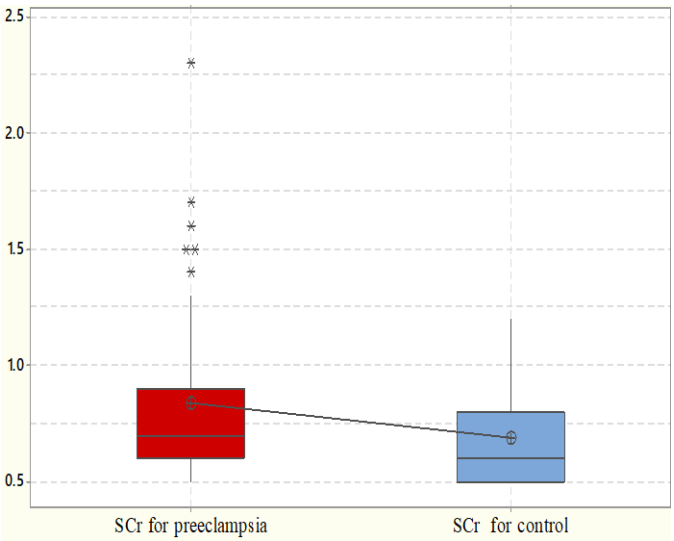

Figure 2: Boxplot for Serum Creatinine between pre-eclampsia and control groups.

SCR: Serum Creatinine

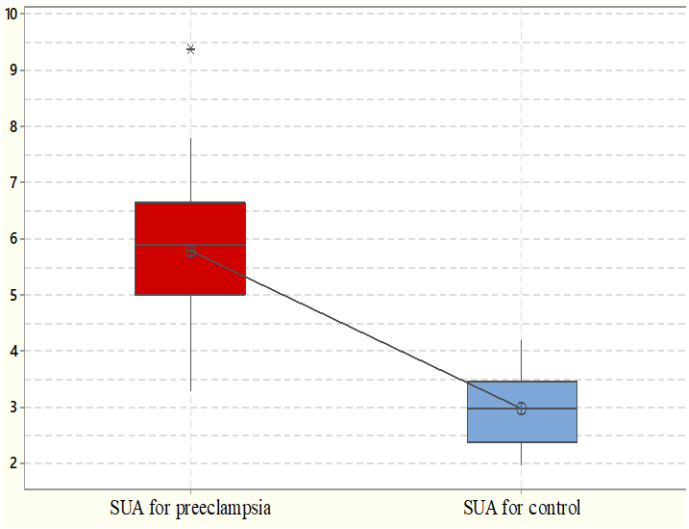

Figure 3: Boxplot for Serum Uric Acid between pre-eclampsia and control groups.

SUA: Serum Uric Acid

DISCUSSION

For a long time, preeclampsia has been a dreaded disease that affects women and their pregnancies. The illness could lead to a slew of difficulties for both the mother and the unborn kid. This has caused anxiety in some expecting mothers and piqued the interest of obstetricians all over the world [14,38]. found that the development of preeclampsia is a complex process involving multiorgan failure, with no single factor being strictly necessary or sufficient to cause it. It raises the risk of obstetric complications such as placental abruption, premature labor, eclampsia, and Hellp syndrome. Glomerular endothelial damage causes a decrease in Glomerular filtration rate (GFR) in several conditions, according to [11].

The term glomerular endotheliosis has been used to describe the ultrastructural changes in renal glomeruli, including generalized swelling and vacuolization of the endothelial cells and loss of the capillary space [39,40]. There are subendothelial deposits of fibrin that decrease the filtration surface area. Electron microscopy shows loss of glomerular endothelial fenestrae, which leads to a 40% decline in glomerular filtration rate [40,41]. Although glomerular endotheliosis was once considered pathognomonic for preeclampsia, recent studies have shown that trace to mild glomerular endotheliosis may also occur at term during normal pregnancy. This finding suggests that the endothelial dysfunction of preeclampsia may be an exaggeration of a normal physiological process that occurs near the end of pregnancy [40,42].

In our current study, we noticed a significant increase in the level of uric acid in the preeclampsia group (5.80 ± 1.13 mg/dL) compared to the control group (2.982 ± 0.672 mg/dL), and serum urea in the preeclampsia group (29.6 ± 13.8 mg/dL) compared to the control group (20.50 ± 2.70 mg/dL).

Our results are in line with those of both [14] that showed that the mean plasma urea and uric acid levels were significantly raised ($p<0.05$) among the preeclamptic population when compared with normotensive pregnant women and [10] reported an increase in the mean uric acid and creatinine values in preeclampsia compared to in pregnancy-induced hypertension and in normal pregnancy with a p-value <0.001. In a study by [17] it was discovered that serum urea and uric acid levels were considerably higher in both study groups (pregnant women presenting with preeclampsia at the age < 35 years and pregnant women presenting with preeclampsia at the age ≥35 years). [43,44] found that the preeclampsia test group had a substantial increase in serum uric acid when compared to the normotensive control group. [45-48] found that uric acid and urea levels are considerably elevated $P<0.001$ levels. The degree of rising in serum uric acid level in preeclamptic was discovered to be a predictor for the severity of this illness in various investigations. Elevated serum uric acid levels have also been interpreted to act as an important cofactor involved in the pathogenesis and manifestation of the pre-eclamptic disorder.[29] showed a significant increase in serum urea level in the preeclampsia (case) group compared to the normal pregnant (control) group. [49] in their study found an increase in serum uric acid level in preeclampsia compared to pregnancy induced hypertension group and healthy pregnant women with p value <0.001.

In contrast to our findings, [35] concluded that the differences in mean serum uric acid (SUA) concentrations between preeclamptic and normotensives were not statistically significant, and that this parameter had limited utility in the prediction of preeclampsia. Furthermore, the small difference in serum urea (SU) levels between pre-eclamptics and normotensives was not significant. There was no significant difference in serum urea levels between preeclamptic and normotensive pregnant women, according to [33]. In their research [50,51] they found that modest changes in SU levels in pre-eclamptic and normotensives are inconsequential.

In this study, there were no statistically significant variations in serum creatinine between the preeclampsia and control groups, which were (0.8420.346), (0.7980.312), respectively. [17] discovered that both research groups (pregnant women presenting with preeclampsia in age <35 years and age ≥35 years.) had normal mean creatinine levels with no significant differences in mean values. As a result, its findings matched what we discovered in our research. [35] showed the differences in mean serum creatinine (SCr) concentrations between preeclamptics and normotensives were not statistically significant, indicating that these markers have limited use in predicting preeclampsia. [52] discovered that there was no significant difference in serum creatinine levels between preeclamptic and normotensive pregnant women.

In contrast to our findings, [10,14]. found that the mean plasma Creatinine level in preeclamptic women was substantially higher ($p<0.05$) than in normotensive control pregnant women. When comparing preeclamptic and normotensive pregnant women, [33] discovered that serum creatinine was considerably greater in preeclamptic women. In the two indicated groups (the preeclamptics and the normotensives), [43,51] found no significant change in Serum Creatinine (SCr).

[45-48] found that serum creatinine levels are considerably higher at $P<0.001$ levels. The preeclampsia (case) group had a significantly higher serum creatinine level than the typical pregnant (control) group, according to [29]. In their study, [49] discovered that preeclampsia patients had higher serum creatinine levels than pregnancy-induced hypertension patients and healthy pregnant women, with a p- value of <0.001. With a statistically significant p- value of <0.001, [53] discovered a rise in serum creatinine level in preeclamptic group compared to high-risk group and normal pregnant control group. Positive relationships ($p<0.05$) were seen between serum urea and serum creatinine, but none between serum creatinine and serum uric acid, or between serum urea and serum uric acid.

Uric acid is a purine catabolite metabolite end product. In a normal pregnancy, uric acid content drops by 25% to 35%, owing to estrogen, increased blood volume, and higher glomerular filtration rate (GFR) [14,54] However, it later rises to a nonpregnant women level at term. However, in preeclamptic patients, uric acid tends to increase much earlier than the onset of hypertension and proteinuria [14,55] and fall in GFR [14,56].

Previous study suggested that hyperuricemia in Preeclampsia is multifactorial [11,34]. In Preeclampsia, elevated levels of uric acid are not only attributed to decreased renal excretion but also to antioxidant effect in response to oxidative stress resulting from placental ischemia and increased activity of xanthine oxidase enzyme [11,14,57]. This may be protective on one hand; Uric acid (as also creatinine and to some extent urea), possessing water-soluble or hydrophilic antioxidant characteristics, may delay or inhibit cellular damage mainly through the free radical scavenging property; it also presents strong antioxidant activity towards Reactive oxygen species (ROS) in the aqueous phase. Uric Acid contributes to about 60% of free radical scavenging activity in human serum [35,58]. the observed uric acid elevation may be a protective response, capable of opposing harmful effects of free radical activity and oxidative stress [35,59].

Increased reabsorption and decreased excretion of uric acid in proximal tubules, comparable to the physiologic response to hypovolemia, is one of the principal causes of elevated serum uric acid. Increased serum uric acid levels could also suggest the presence of undiscovered subclinical renal impairment in some women, thereby increasing the risk of preeclampsia [35]. Hyperuricemia, on the other hand, has been demonstrated to have a proinflammatory effect that can lead to endothelia dysfunction [14,60]. possibly causing vascular damage and hypertension [14,61,62], As a result, the situation has gotten worse. Recent research has revealed a link between serum uric acid and the severity of preeclampsia [14, 34,63]. According to [11,43] a single measurement of serum uric acid level early in pregnancy has limited benefit in predicting pre-eclampsia. [11,64] on the other hand, found serum uric acid to be an inaccurate predictor of developing hypertension in individual women.

In normal pregnancy, the glomerular filtration rate increases than the normal level and it eventually decreases the level of serum creatinine, urea and uric acid [17,65]. Various studies suggest that hypo perfusion leads to decrease in glomerular filtration rate in preeclampsia coupled with abnormal renal tubular function, results in increase in serum creatinine and blood urea level. The increase in blood urea level is also due to micro-angiopathic hemolysis that occurs due to maternal endothelial dysfunction leading to increase synthesis of urea in the body [3,29,53].

Some investigators found that the activity of mono amino oxidase (MAO) is lower and serotonin is higher in the placental tissue from women with preeclampsia as compared with placental tissue from normal pregnant women [45,66,67]. these

factors lead to a reduction in renal perfusion in a woman with preeclampsia, by an average of 20% and reduction in GFR by an average of 32% in comparison with normal pregnant women near term So, as a result of reduced GFR, serum creatinine levels and blood urea rise above normal pregnancy levels [45]. Changes in renal parameters were attributed to an increase in glomerular filtration resistance in preeclampsia due to the mechanical effect of swelling in the cytoplasm, as well as a change in metabolism, resulting in a reduction in renal perfusion and the glomerular filtration rate, according to their findings [5,33].

CONCLUSION

Preeclampsia has negative effects on renal function parameters, according to a current study. While there was no significant difference in serum creatinine, there was a substantial increase in serum uric acid and serum urea levels in preeclamptic patients compared to normal pregnancy. These variables can be used to predict the disease. As a result, in preeclampsia, monitoring renal parameters such as serum uric acid and serum urea is critical for reducing maternal and fetal death and morbidity. Close monitoring of these variables will also aid in the prevention of future issues in these patients. Our study's limitation is the small sample size.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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