International Journal of Biochemistry Research & Review

Volume 31, Issue 10, Page 1-10, 2022; Article no.IJBCRR.93364
ISSN: 2231-086X, NLM ID: 101654445

Inflammatory Mediators (CA125, CRP) and Uric Acid in Association with Severity of Preeclampsia in North Kordofan State, Western Sudan

Naglaa Abdelbasit Suliman [a], Khidir Elamin Awadalla [b], Khalid Hussein Bakheit [c*] and Abdelrahim Osman Mohamed [d]

[a] Department of Biochmistry, Faculty of Medicine, University of Kordofan, Sudan.
[b] Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Kordofan, Sudan.
[c] Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Kingdom of Saudi Arabia.
[d] Department of Biochemistry, Faculty of Medicine, University of Khartoum, Sudan.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJBCRR/2022/v31i10781

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/93364

Original Research Article

Received: 27/08/2022
Accepted: 02/11/2022
Published: 04/11/2022

ABSTRACT

Introduction: Inflammatory mediators could be laboratory markers of preeclampsia, as the induction of an inflammatory process within the placenta may trigger the expression of cancer antigen 125(CA125), C-reactive protein (CRP) and uric acid (UA). Regarding the pathophysiology of pre-eclampsia, there is defective trophoblastic invasion of uteroplacental blood vessels that leads to placental ischemia, and induction of an inflammatory process within the placenta.
Objective: To evaluate the association of serum levels of cancer antigen (CA125), C-reactive protein (CRP) and serum uric acid with the Severity of Preeclampsia.

**Corresponding author: E-mail: khalid2_3456@yahoo.com;*

Materials and Methods: The study recruited 200 singleton Sudanese pregnant women. These participants were divided into two groups: control (n = 100) and cases (n = 100). The cases were further subdivided into; mild preeclampsia (n =46), and severe preeclampsia (n = 54). The study groups were well-matched in maternal age, gestational age and body mass index. Blood samples were taken for measurement of serum cancer antigen-CA125, uric acid and C - reactive protein using immune- assay and enzymatic automated chemical analysis.
Results: The mean levels of cancer antigen-CA125 in mild and severe preeclampsia groups were; 21.94±5.08 (IU/ml) and 40.77±9.82 (IU/ml) respectively, which were significantly higher, (*P*<0.001) in comparison with the control group (16.88±7.36 (IU/ml). The mean levels of C-reactive protein in mild and severe preeclampsia were; 15.17±5.35 (mg/L), 31.49±12.56 (mg/L) respectively. There was significant difference in their levels, compared to the control group (4.79±1.78 (mg/L), (*P*<0.01). Also, the mean levels of uric acid in mild and severe cases were; 6.44±1.98 and 7.37±2.00 which was significantly higher, in comparison with the control (4.00±0.61); (*P<0*.001). The level of uric acid also, showed significant difference within the case (severe and mild) group (*P<0*.05). CA125, CRP and UA levels correlated positively with Mean Arterial blood pressure (MAP), (r>0.7; *P* < 0.001). ROC curve validate the utility of these biomarker for the detection of preeclampsia severity (AUC>0. 8; *P* < 0.001).
Conclusion: Serum cancer antigen 125(CA125), C- reactive protein and uric acid in studied preeclampsia groups were found to be significantly higher compared with the control group, and the rises were directly associated with the severity of preeclampsia.

Keywords: Cancer antigen; C-reactive protein; uric acid; preeclampsia (PE); Sudan.

1. INTRODUCTION

"Preeclampsia(PE) is a pregnancy-specific hypertensive disorder with multi- system involvement, that originates in the placenta" [1,2]. "PE remains the main cause of variable maternal and fetal morbidity and mortality in the developing countries [3]. It complicates approximately 5 – 8 % of all pregnancies" [4]. "It is characterized by the onset of hypertension (BP ≥140/90 mm Hg) and significant proteinuria (300 mg protein per day), occurring after the 20th week of pregnancy, in previously normotensive women" [5]. Many theories suggested its pathophysiology; including the failure of trophoblast invasion of uterine spiral arterioles, causing placental ischemia, which triggers the expression of inflammatory factors in maternal circulation, that may result in endothelial dysfunction, which specifically gives the clinical picture of preeclampsia [6,7]. "It is associated with increased systemic vascular resistance, enhanced platelet aggregation and activation of the coagulation system" [8–12].

The inflated maternal inflammatory response responsible for endothelial dysfunction, may trigger expression of cancer antigen (CA125) and C-reactive protein (CRP).

"Cancer antigen-125 (CA-125) is a high molecular weight glycoprotein complex antigen, expressed by epithelial ovarian tumor [13,14]. CA 125 is a marker of peritoneal and pleural disease" [15], and was detected in the serum in many physiological and pathological conditions [16,17]. "The extension of decidual destruction and separation of trophoblast from decidua, are anticipated as the primary means for the elevation of serum (CA-125) in preeclampsia" [18,19]. "It's role in obstetrics is not fully clarified, as most clinical trials recommending its use are generally experimental in nature. There are few clinical studies related to the use of CA-125 in hypertensive disorders of pregnancy with conflicting results" [20]. "However, some studies reported positive correlation between serum CA125 concentration and preeclampsia" [21–24].

"C - reactive protein (CRP) is an acute phase protein produced by hepatocyte in response to release of Pro-inflammatory cytokines. It is a sensitive marker of systemic inflammation" [22], responsible for the endothelial dysfunction in preeclampsia [25]. Many studies reported its sensitivity and specificity in the prediction of PE [26–30].

"Uric acid (UA) is a major end -product of purine catabolism" [31]. "Hyperuricemia is the most consistent and earliest detectable changes in preeclampsia, and was reported as a better predictor of fetal risk" [32–35]. "Hyperuricemia has been related to cardiovascular and renal diseases through the generation of reactive oxygen species (ROS), and subsequent endothelial dysfunction" [33,34,36–38]. Another study, revealed that, the level of serum uric acid

was not steadily elevated in all women with severe preeclampsia, suggesting that the uric acid was not a useful predictive test for PE [39].

According to the inconsistent results revealed by some previous works, we designed this study to measure the level of cancer antigen-125 (CA-125), (CRP) and (UA) and to determine their association with the severity of preeclampsia in Sudanese pregnant women.

2. MATERIALS AND METHODS

The study was conducted at Elobeid teaching hospital, North Kordofan State, Western Sudan during period from December 2017 to December 2020. Hundred patients with preeclampsia attending the antenatal ward and delivery room, in the age range (15-50) years, who fulfilled the criteria for pre-eclampsia were approached to participate in the study as cases. They were further divided into mild (46), and severe preeclampsia (54) according to the diastolic blood pressure (<110 or ≥110mmHg, and systolic blood pressures<160 or ≥160mmHg) respectively [40]. A number of 100 normotensive pregnant women, presenting to the same outpatient clinics, were recruited as control group. Both groups were in the second half of pregnancy. Gestational age was calculated from the last menstrual period, and confirmed by early first trimester ultrasound reports in suspected cases. Blood pressure was measured for all patients and controls with mercury sphygmomanometer. Patients having persistent high blood pressure ≥140/90 mmHg on 2 or more occasions 6 hours apart, with proteinuria ≥ +2 by dipstick, or ≥300 mg/day in 24 hours' urine collection were chosen for this study. Mean arterial blood pressure (MABP) for each subject was determined by the formula MABP [Diastolic blood pressure + (systolic blood pressure – diastolic blood pressure)/3].

Women with a history of ovarian, endometrial, or breast cancer, or benign conditions such as endometriosis, multiple pregnancies, medical disorders such as diabetes mellitus, chronic hypertension, liver, renal, and cardiovascular disease, or inflammatory conditions were excluded from the study. Structured questionnaire was used to gather socio-demographic characteristics.

2.1 Sample Collection

Five ml of venous blood was collected from both groups by venipuncture in plain tubes. Samples were kept at room temperature for 30 minutes to clot, and were then centrifuged at 2000 rpm for 10 minutes, and serum was stored at -20 C° until the assay.

2.2 Inflammatory Mediators Measurement

The serum level of cancer antigen-125 (CA-125), was measured for both patient and control groups by automated chemical analyzer; (Mindary CL-1200iChemiluminescene Immunoassay System-India), using antigen – antibody reaction**.** Serum (CRP) and UA levels were measured by; (Mindary Bs200 Automated Benchtop Chemistry Analyzer-India), using enzymatic reaction according to the manufacturer's instructions.

2.3 Statistics Analysis

Data was entered, coded and analyzed using statistical package for social sciences version 20 software (SPSS Software, Chicago Inc., USA). Data was expressed as mean ± SD. The t-test was used to compare the two groups (cases and controls). While One-way ANOVA was used to compare the parametric variables of the three groups (control, mild, and severe preeclampsia). *P* value of <0.05 was considered significant. Pearson correlation was done to find correlation coefficient value (r), either positive (direct correlation), or negative (in verse correlation), with value < 0.3 represents no correlation, 0.3 - <0.5 represents weak correlation, 0.5 - < 0.7 represents moderate correlation, and > 0.7represents strong correlation. Multiple Receiver Operating Characteristic curve (ROC) was drawn to evaluate validity of CA125, CRP and UA in predicting pregnant women at risk of preeclampsia disease, and its severity. The test was considering good marker if it showed area under the curve (AUC ≥0.8).

3. RESULTS

A total of 200 pregnant women; (100) cases of PE, and (100) controls, were recruited during the study period. Socio-demographic and obstetric data of the studied women are described in Table 1. Both groups were matched in age, body mass index and gestational age among PE patients with respect to the normotensive pregnant women.

There was no significant difference (*P*>0.*05*) in the maternal age, BMI, and gestational age.

Regarding, the mean levels of CA-125, CRP and UA, they were statistically significantly higher in severe and mild PE group in comparison with the control group (p<0.001) The mean level of UA also, was significantly different in severe and mild PE group in comparison with the control group(p<0.05) as shown in Table 2.

Table 1. Clinical and demographic characteristic of the patient's groups (mild and severe preeclampsia) and control group

Variables	Control (n=100) Mean ±SD	Mild PE (n=46) Mean ±SD	Severe PE (n=54) Mean ±SD	P-Value
Age(years)	26.67± 6.74	26.68± 6.31	26.33±7.47	0.987
BMI	26.78± 4.02	27.56± 4.97	27.93± 4.49	0.145
Gestational age (weeks)	33.67± 4.59	33.82± 3.81	34.46± 4.96	0.641

Table 2. (Mean ±SD) of serum cancer antigen (CA125), CRP, UA and MAP in the patient's group and control groups

Variables	Control (n=100) Mean ±SD	Mild PE (n=46) Mean ±SD	Severe PE (n=54) Mean ±SD	P- value
CA125	16.48± 5.84	21.94± 5.08	40.78± 9.82	< 0.001
CRP	4.79±1.78	15.17±5.35	31.50±12.56	< 0.001
UA	4.00±0.61	6.44±1.98	7.37±2.00	< 0.05
MAP	84.15±9.6	115.89±5.95	136.06±8.92	< 0.001

Table 3. The coefficient correlation(r) of CA-125, CRP and UA with MAP in preeclampsia

Parameters	Coefficient correlation(r)	*P*-value
CA125	0.771	
CRP	0.808	0.001
UA	711	

Our study revealed a strong positive correlation between CA-125, CRP and UA levels and Mean Arterial blood; (r> 0.7, P < 0.001)

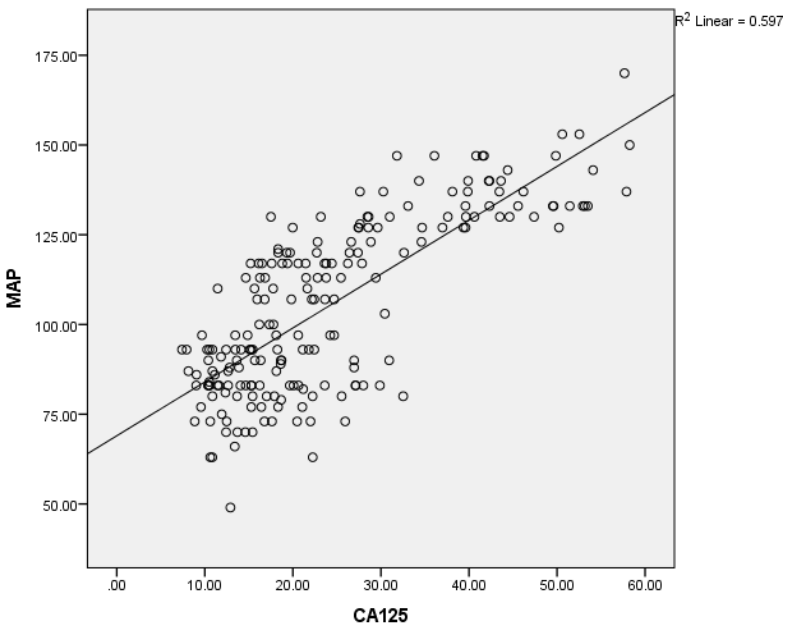

Fig. 1. Significant correlation of CA125 and MAP in the study groups (mild and severe preeclampsia)

MAP = 40 + 2.333 CA125 (regression equation according to coefficients table) (t = 17.11, p < 0.001)

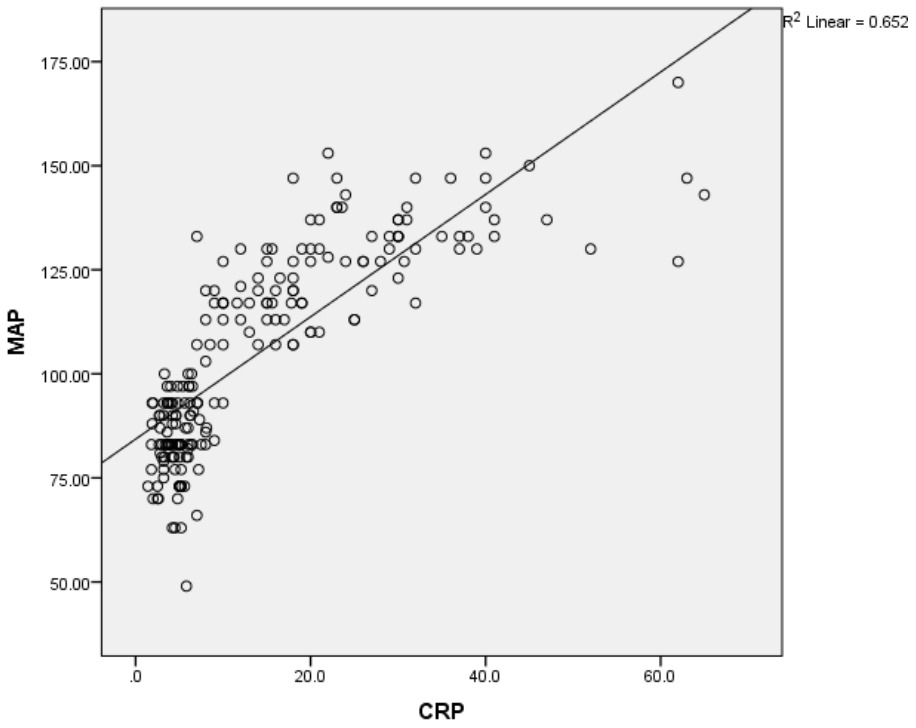

Fig. 2. Significant correlation of CRP and MAP in the study groups (mild and severe preeclampsia)

MAP = 40 + 2 CRP (regression equation according to coefficients table) (t = 19.27, p < 0.001)

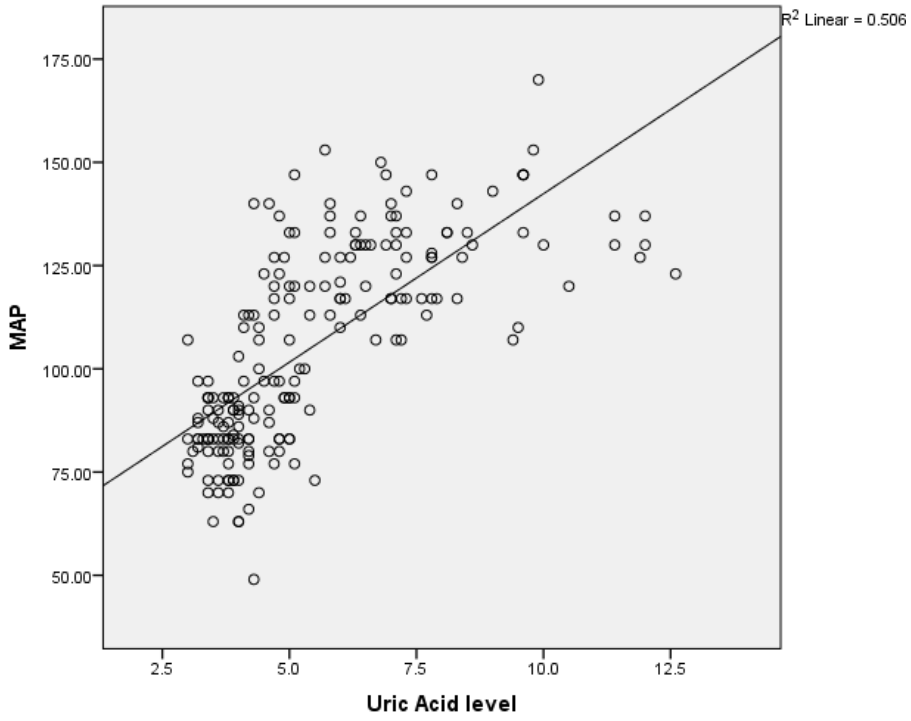

Fig. 3. Significant correlation of UA and MAP in the study groups (mild and severe preeclampsia)

MAP = 16.6667+11.6667 UA (regression equation according to coefficients table) (t = 14.24, p < 0.001)

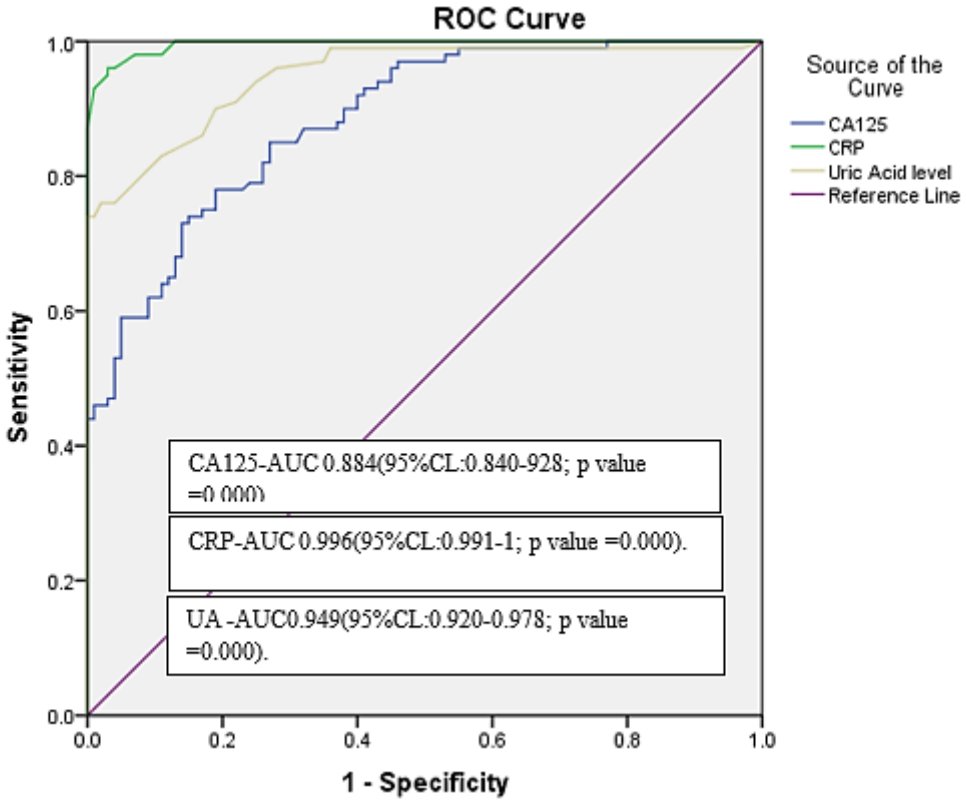

Fig. 4. ROC curve of serum CA125, CRP and UA levels in preeclampsia

According, to the Pearson coefficient correlation test, MAP was found to have a significant effect on the increase in CA125, CRP and UA in preeclampsia as shown in Figs. 1, 2 and 3 respectively.

Multiple Receiver Operating Characteristic curve was drawn to evaluate validity of CA125, CRP and UA in predicting pregnant women at risk of preeclampsia disease and its severity. As shown in Fig. 4.

The sensitivity of CA125 was (85%), the specificity was (73%), while the sensitivity of C – reactive protein was (95%), the specificity was (97%), and sensitivity of Uric acid was (86%), the specificity was (83%).

4. DISCUSSION

"Pre-eclampsia is a multisystem disorder of unknown etiology, that constitutes a major cause of maternal, and fetal morbidity and mortality worldwide" [41,42].

In the present study, demographic data of the patient and control groups, showed no significant differences with respect to maternal age, gestational age, and BMI. confirming the demographic equivalence in the two groups (patient and control).

"In the current study preeclampsia was found to be associated with an increased level of CA125, CRP and UA among patients in comparison with controls group. The CA-125 levels were significantly higher in severe and mild PE in comparison with the control group ($p<0.001$); CA-125 levels were higher in severe preeclampsia when compared to mild preeclampsia($p<0.001$), and this suggests the association of its level with preeclampsia severity. Our study revealed a strong positive correlation between CA-125 levels and Mean Arterial blood pressure(MAP) in preeclampsia ($r> 0.7$, $P < 0.001$), as demonstrated in Fig. 1 which is consistent with previous studies stated by other authors" [28,43].

Receiver operating characteristic (ROC) curve of serum CA125 in preeclampsia indicating the validity of CA125 as a sensitive and specific prognostic tool for the prediction of PE severity; (AUC>0.8; P<0.001) as shown in Fig. 4. The

elevation of CA-125 in PE patients in this study agreed with many previous studies [21,23,28,44], in which some authors suggesting that CA125 is a promising biochemical marker, and can reflect the severity of preeclampsia [7,11,18,21,23, 28,43,45–47]. "This rising level of CA-125, might be due to failure of trophoblastic invasion, and the induction of an inflammatory process within placenta, that triggers the expression of CA-125. In contrast to our result Schro¨cksnadel et al. [16] and Bon et al. [20] found no statistically significant difference in CA- 125 between patients and control groups". This inconsistence finding with our result might be due to different sample size, demographic and genetic variations, and different timing of CA125 measurement during pregnancy. In addition, the variable degrees of failure of trophoblast invasion, might be a causative factor of such variation in biochemical markers levels.

Moreover, our study showed an elevation in the mean level of CRP in mild and severe PE patients in comparison with the control group ($p<0.001$), and these escalations directly correlated with the severity of preeclampsia ($p<0.001$). This finding is in agreement with that obtained previously by many authors [24,27–30,47], where serum CRP was significantly positively correlated with MAP($r>0.7$, $p<0.001$). As systemic inflammatory response is one of pathophysiological mechanisms of PE, CRP was more sensitive and specific to predict PE in pregnant women (AUC= 0.9) Fig. 4. The increment in CRP was directly correlated with the severity of the disease; hence it can be used for early prediction of severity of PE. However, contrasting studies [26,48] found no association between the maternal inflammatory mediator CRP and established PE.

"Furthermore, the study indicated significantly higher difference in the mean values of UA level in the patient's group (mild and severe) in comparison with the control group ($p<0.001$), and significant different between severe and mild ($P>0.05$). UA showed strong positive correlation with MAP ($r>0.7$, $P<0.001$) and (AUC= 0.94) as illustrated in Fig. 4. This elevated- serum uric acid levels was consistent with other reported results" [34,49,50]. "Soluble uric acid impairs the vasodilating-nitric oxide generation in endothelial cells inducing endothelial dysfunction and pre-eclampsia" [37]. Recent evidence [51], "supports a role for uric acid as a true cardiovascular risk factor, particularly for the development of hypertension and renal disease" [49,52]. The rise in uric acid level in preeclampsia is due to placental injury, which causes purine catabolism and uric acid generation. However, our finding is contradicted with others who reported that high level of serum uric acid was not consistently found elevated in all women with severe preeclampsia, suggesting that the uric acid could not be a useful prognostic test as stated by Amat-Al Karem [39]. However, Kanti Mandal et al. [53] stated that serum UA and CRP may be possible to use as biomarkers for identifying women at risk of Preeclampsia.

"This study also revealed a strong positive correlation between CA-125, CRP and UA levels and Mean Arterial blood pressure(MAP) in preeclampsia ($r> 0.7$, $P < 0.001$) as demonstrated in (Figs. 1, 2 and 3) which was consistent with previous studies stated by other authors" [43,28].

According to the results of specificity and sensitivity of CRP and CA 125, levels obtained in the current study, emphasizes the potential role these markers as predictive test for severity of PE.

Additionally, our study indicates that CA-125 can be used as a marker in preeclampsia follow-up. Since it is much more available and comparatively less expensive, it seems to be a promising test for screening preeclampsia.

5. CONCLUSION

Our study demonstrated increased levels of CA-125, CRP and UA levels in women with preeclampsia, which were correlated with the severity of the disease. This study suggested that CRP and CA-125 are biochemical markers which reflects the severity of the inflammatory process in preeclampsia. Similarly, UA may be a useful biomarker for identifying women at risk of preeclampsia.

6. LIMITATIONS

Our study is hospital-based limited by the availability of patients; therefore, a convenient sample size might be under representative to the general population, researches with large sample size and at different gestational ages are needed to clear up the association of elevated serum CA-125 level in Sudanese women with severe preeclampsia.

CONSENT AND ETHICAL APPROVAL

A written informed consent was obtained from all participants. The ethical clearance was obtained from ministry of health, North Kordofan State-Sudan, and research board at the faculty of medicine, university of Kordofan.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Vatten LJ, Skjærven R. Is pre-eclampsia more than one disease? BJOG An Int J Obstet Gynaecol. 2004;111(4):298–302.
2. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science (80-). 2005;308(5728):1592–4.
3. Craici IM, Wagner SJ, Weissgerber TL, Grande JP, Garovic VD. Advances in the pathophysiology of pre-eclampsia and related podocyte injury. Kidney Int. 2014;86(2).
4. Phipps E, Prasanna D, Brima W, Jim B. Preeclampsia: Updates in pathogenesis, definitions, and guidelines. Clin J Am Soc Nephrol. 2016;11(6):1102–13.
5. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet [Internet]. 2005; 365(9461):785–99.
6. Jim B, Karumanchi SA. Preeclampsia: Pathogenesis, prevention, and long-term complications. Semin Nephrol. 2017;37(4).
7. De Groot CJM, O'Brien TJ, Taylor RN. Biochemical evidence of impaired trophoblastic invasion of decidual stroma in women destined to have preeclampsia. Am J Obstet Gynecol. 1996;175(1):24–9.
8. Phipps E, Prasanna D, Brima W, Jim B, Einstein A. Mini-review preeclampsia : Updates in pathogenesis, definitions, and guidelines. 2016;11(6).
9. Poston L. Endothelial dysfunction in pre-eclampsia. Pharmacol Reports. 2006;58(SUPPL.):69–74.
10. Palei AC, Spradley FT, Warrington JP, George EM, Granger JP. Pathophysiology of hypertension in pre-eclampsia: A lesson in integrative physiology. Acta Physiol. 2013;208(3):224–33.
11. Roberts JM, Hubel CA. The two stage model of preeclampsia: Variations on the theme. Placenta [Internet]. 2009; 30(SUPPL.):32–7.
12. Hladunewich M, Karumanchi SA, Lafayette RA. Pathophysiology of the clinical manifestations of preeclampsia. Clin J Am Soc Nephrol. 2007;2(3):543–9.
13. Santulli P, Streuli I, Melonio I, Marcellin L, M'Baye M, Bititi A, et al. Increased serum cancer antigen-125 is a marker for severity of deep endometriosis. J Minim Invasive Gynecol [Internet]. 2015;22(2):275–84.
14. Muyldermans M, Cornillie FJ, Koninckx PR. Ca125 and endometriosis. Hum Reprod Update. 1995;1(2):173–87.
15. No A. Human peritoneal mesothelial cells are more potent than ovarian cancer cells in producing tumor marker CA-125 1. 1996;389:384–9.
16. Schrocksnadel H, Daxenbichler G, Artner E, Steckel-Berger G, Dapunt O. Tumor markers in hypertensive disorders of pregnancy. Gynecol Obstet Invest. 1993;35(4):204–8.
17. Gadducci A, Cosio S, Carpi A, Nicolini A, Genazzani AR. Serum tumor markers in the management of ovarian, endometrial and cervical cancer. Biomed Pharmacother. 2004;58(1):24–38.
18. Medicine A. Determination of cancer antigen-125 level and its association with preeclampsia among Sudanese women. Ann Clin Anal Med. 2020;11(9):416–9.
19. Tyler C, Kapur A, Felder M, Belisle JA, Trautman C, Gubbels JAA, et al. The Mucin MUC16 (CA125) binds to NK cells and monocytes from peripheral blood of women with healthy pregnancy and preeclampsia. Am J Reprod Immunol. 2012;68(1):28–37.
20. Bon GG, Kenemans P, Verstraeten AA, Go S, Philipi PA, Van Kamp GJ, et al. Maternal serum CA125 and CA15-3 antigen levels in normal and pathological pregnancy. Fetal Diagn Ther. 2001; 16(3):166–72.
21. Osanyin GE, Okunade KS, Ayotunde Oluwole A. Association between serum CA125 levels in preeclampsia and its severity among women in Lagos, South-West Nigeria. Hypertens Pregnancy [Internet]. 2018;37(2):93–7.
22. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of inflammation and infection. 2018;9(April):1–11.
23. Bellos I, Pergialiotis V, Loutradis D, Papapanagiotou A, Daskalakis G. Serum CA-125 levels in preeclampsia: A systematic review and meta-analysis. Int J Clin Pract. 2019;73(10):1–7.

24. Kamel M, Ch MBB. The association of serum cancer antigen 125 and C - reactive protein level with the severity of preeclampsia. 2012;5(1).
25. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003;107(3):363–9.
26. Savvidou MD, Lees CC, Parra M, Hingorani AD, Nicolaides KH. Levels of C-reactive protein in pregnant women who subsequently develop pre-eclampsia. BJOG An Int J Obstet Gynaecol. 2002;109(3):297–301.
27. Kholeif AE, Khamis MY, Eltabakh S, Swilam RS, Elhabashy A, ElSherif R. Prediction of severity of preeclampsia in Egyptian patients: Role of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and C-reactive protein. Clin Exp Obstet Gynecol. 2020;47(2):183–8.
28. Cebesoy FB, Balat O, Dikensoy E, Kalayci H, Ibar Y. CA-125 and CRP are elevated in preeclampsia. Hypertens Pregnancy. 2009;28(2):201–11.
29. Qiu C, Luthy DA, Zhang C, Walsh SW, Leisenring WM, Williams MA. A prospective study of maternal serum C-reactive protein concentrations and risk of preeclampsia. Am J Hypertens. 2004;17(2):154–60.
30. Üstün Y, Engin-Üstün Y, Kamaci M. Association of fibrinogen and C-reactive protein with severity of preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2005;121(2):154–8.
31. Fay RA. Uric acid in pregnancy and preeclampsia: An alternative hypothesis. Aust New Zeal J Obstet Gynaecol. 1990;30(2):141–2.
32. Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, et al. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. Hypertension. 2005;46(6): 1263–9.
33. Jeyabalan A, Conrad KP. Renal function during normal pregnancy and preeclampsia. Front Biosci. 2007;12(7): 2425–37.
34. Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in preeclampsia. Placenta. 2008;29(SUPPL.):67–72.
35. Ugwuanyi RU, Chiege IM, Agwu FE, Eleje GU, Ifediorah NM. Association between serum uric acid levels and perinatal outcome in women with preeclampsia. 2021;2021.
36. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003;41(6):1183–90.
37. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int. 2005;67(5):1739–42.
38. Maruhashi T, Hisatome I, Kihara Y, Higashi Y. Hyperuricemia and endothelial function : From molecular background to clinical perspectives. Atherosclerosis [Internet]. 2018; 278(October):226–31.
39. Ah AK, Huri A, Shuaib AA, Harazi AH Al. Serum uric acid in women with preeclampsia compared to normotensive women. 2016;52(3):114–9.
40. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertens [Internet]. 2013;3(1):44–7.
41. Von Dadelszen P, Magee LA. Pre-eclampsia: An Update. Curr Hypertens Rep. 2014;16(8).
42. Tomimatsu T, Mimura K, Matsuzaki S, Endo M, Kumasawa K, Kimura T. Preeclampsia: Maternal systemic vascular disorder caused by generalized endothelial dysfunction due to placental antiangiogenic factors. Int J Mol Sci. 2019;20(17):1–18.
43. Ozat M, Kanat-Pektas M, Yenicesu O, Gungor T, Danisman N, Mollamahmutoglu L. Serum concentrations of CA-125 in normal and preeclamptic pregnancies. Arch Gynecol Obstet. 2011;284(3):607–12.
44. Medicine A. Determination of cancer antigen-125 level and its association with preeclampsia among Sudanese women 2020;11(9):416-419.
45. Mollamahmutoglu L. S of CA-125 in normal and preeclamptic pregnancies. 2010; (November);254(3):607-612.
46. Han A, Yıldırım G, Karaman E, Karaman Y. Pregnancy hypertension. An International Journal of Women ' s Cardiovascular Health Maternal serum CA-125 level is elevated in severe preeclampsia. 2014;4:29–33.

47. Ibrahem W, Kh. Al-Assaly R, Saeed Al-Haddad N. CA-125, plasma fibrinogen and C-reactive protein in correlation with severity of preeclampsia. J Fac Med. 2017;59(1):31–5.
48. Stefanović M, Vukomanović P, Milosavljević M, Kutlešić R, Popović J, Tubić-Pavlović A. Insulin resistance and c-reactive protein in pre eclampsia. Bosn J Basic Med Sci. 2009;9(3):235–8.
49. Martin AC, Brown MA. Could uric acid have a pathogenic role in pre-eclampsia? Nat Rev Nephrol. 2010; 6(12):744–8.
50. Report B. Patients with severe preeclampsia. 2003;28(4):198–9.
51. Leanza A, Molino G. Hyperhomocysteinemia in preeclampsia is associated to higher risk pressure profiles. 2003;81–7.
52. Pipkin FB. Uric acid, endothelial dysfunction and pre-eclampsia. J Hypertens. 2004;22(2):237–9.
53. Kanti Mandal D, Premchandra Singh Y, Das D, Sangeeta Devi N, Singh Nn, Singh Wg. Serum uric acid and c-reactive protein in preeclampsia. IOSR J Dent Med Sci Obs Gynae, Reg Inst Med Sci [Internet]. 2015;14(2):2279–853.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/93364