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Beta-2-microglubulin levels in preeclamptic patients in Benin City, Nigeria

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Abstract

Preeclampsia is a condition accompanied by elevated blood pressure and proteinuria thus suggestive of cardiac and renal dysfunctions. Plasma urea and plasma creatinine are known as gold standards that provide insights into kidney function and potential renal involvement in preeclampsia. In preeclamptic women, an elevation in plasma urea and creatinine levels can indicate impairment in kidney function and reduced glomerular filtration. Beta-2-microglobulin (B2M) is a protein found on the surface of body cells that is released into the blood stream as a result of normal cell turnover or certain disease processes. This study therefore aims to determine if Beta-2-microglobulin could be added to the gold standards in indicating that there is a nephropathy during preeclampsia. To do this, a prospective case-control research involving 190 women was carried out. They were divided into three groups: a preeclampsia group, a group which consisted of women with only pregnancy-induced hypertension (PIH); and a group of pregnant women with normal blood pressure. Analyses of demographic data, trimesters, severity of disease and Body Mass Index (BMI) data obtained showed that as the level of severity of preeclampsia increased, there was also a rise in the B2M levels. Perhaps, B2M levels could provide insights in the early determination of nephropathy during preeclampsia and also as an indicator for renal tubular dysfunction.

Keywords: preeclampsia, beta-2-microglobulin, pregnancy-induced-hypertension, urea, creatinine

1. Introduction

Preeclampsia is a potentially serious pregnancy complication characterized by high blood pressure and damage to organs, typically the liver and kidneys. It is thought to occur when the blood vessels that supply the placenta become narrow and constrict, reducing blood flow and leading to high blood pressure. It usually occurs after the 20th week of pregnancy and can affect both the mother and the unborn baby. Common symptoms of preeclampsia include high blood pressure (hypertension) (1, 2, 3), swelling of the hands and face (edema), protein in the urine (proteinuria), severe headaches, blurred vision, and abdominal pain. Preeclampsia can lead to serious complications for both the mother and the baby, such as eclampsia (seizures), organ damage, premature birth, low birth weight, placental abruption (separation of the placenta from the uterus), and even maternal or fetal death. Preeclampsia can pose several risks to both the mother and the unborn baby. Some of the risks associated with preeclampsia include eclampsia, placental disruption, restricted fetal growth, hypertension, cardiovascular disease and kidney problems. Preeclampsia can have significant effects on kidney (renal) function. Some renal malfunctions that can be found in preeclampsia patients include acute kidney injury (AKI), chronic kidney disease (CKD) (4), glomerular injury, proteinuria (5).

There are certain markers which are used as indicators of preeclampsia in pregnant women, they are plasma urea and plasma creatinine. Plasma urea and plasma creatinine are known as gold standards that provide insights into kidney function and potential renal involvement in preeclampsia. . Elevated plasma urea levels may indicate impaired kidney function, as the kidneys are responsible for filtering and excreting urea from the body. Studies have shown that plasma urea levels can be elevated in women with preeclampsia, suggesting renal dysfunction or reduced glomerular filtration rate (GFR) in affected individuals (2). Elevated plasma creatinine levels can indicate impaired kidney function and reduced GFR. Research has shown that preeclamptic women

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may have higher plasma creatinine levels compared to those with normal pregnancies, suggesting kidney dysfunction or decreased renal perfusion (6). Beta-2-microglobulin (B2M) is a protein that is present on the surface of cells in the body, it is a component of major histocompatibility complex (MHC) class 1 molecules, which are involved in immune responses. Beta-2-microglobulin is released into the blood stream as a result of normal cell turnover or certain disease processes. We believe that measurement of beta-2-microglobulin levels in the blood or urine can be used as a diagnostic or prognostic marker for nephropathy specifically as an indicator of renal tubular dysfunction in preeclamptic patients because elevated levels of beta-2-microglobulin are associated with kidney disorders. Beta-2-microglobulin is one of those substances that should normally be reabsorbed by the renal tubules, but in cases of tubular dysfunction, it is excreted in higher amounts in the urine. Measuring the levels of beta-2-microglobulin in urine can help assess the extent of tubular dysfunction and serve as a marker for nephropathy. In this study, we explore the use of beta-2-microglobulin as a potential marker for preeclampsia, particularly in predicting the development of renal complications in the affected patients by using the measurement of urine beta-2-microglobulin in combination with plasma urea and plasma creatinine test to elevate renal function and monitor the progression of nephropathy in preeclampsia patients.

2. Materials and methods

2.1. Ethical approval

Informed consent was obtained from the entire study participant. The nature and aim of this work were fully discussed with the study participants and they had the right to withdraw from the study without being adversely affected regarding the medical service they received. Ethical approval of the ethical committee (Protocol. No. ADM/E.22/A/VOL.VII/1469.), was also obtained from the University of Benin Teaching Hospital.

2.2. Participants and Methods

This study was conducted at the Department of Obstetrics and Gynecology, University of Benin Teaching Hospital and Central Hospital Benin. It was a prospective case-control research involving 190 women. The study participants were divided into three groups: a preeclampsia group (n = 124), a group which consisted of women with only pregnancy-induced hypertension (PIH) (n = 30); and a group of pregnant women with normal blood pressure (n = 36). For the present investigation, maternal illnesses with a history of cardiovascular disease, renal disease, diabetes mellitus, thyroid disease, hepatic disease, or any related disorders including urinary tract infections were excluded. Blood pressure measurements were performed with patients in a prone position on at least two separate occasions with a mercury sphygmomanometer.

The study groups had a single antecubital venipuncture, during which 5ml of venous blood was drawn using a sterile disposable syringe. The obtained whole blood was drawn into a bottle that had been heparinized, instantly separated, and the plasma was collected into a 5 ml plain vial by a Pasteur pipette. The sample was stored at minus 4 degree until ready for analysis. Plasma Beta-2 Microglobulin concentration estimation was by enzyme-linked immunosorbent assay (ELISA) (7).

2.3. Method of data management and statistical analysis

In the present study, statistical analyses of data were carried out using SPSS, version 23 (the Statistical Package for Social Science SPSS Version 23 USA). Data obtained were presented as mean ± standard deviation

3. Results

Proteinuria is a condition marked by the presence of high levels of protein in the urine. Usually, this is detrimental as the urine is expected to have a specific pH and be devoid of proteins. Proteinuria is thus the first pointer to possible nephropathy.

In preeclampsia, the pregnant woman has high levels of protein in her urine, accompanied by elevated blood pressure. During pregnancy, a woman is expected to be healthy although there have been cases of gestational diabetes. One of the major problems with preeclampsia is the elevated blood pressure which results in cardiovascular issues. Proteinuria in pregnant women points out the inability of the mother's kidneys to filter toxins properly which is detrimental to the mother and child alike. Studies have traced preeclampsia to an anomaly in the placenta. Studies have also shown that most times, when attempts are made to treat a preeclampsia patient, such attempts enhance fetal morbidity. The only known cure for preeclampsia at present is to remove the fetus from the womb preterm.

In medicine, the gold standard for determining renal anomalies is the urea and creatinine test. However, studies have begun to link Beta-2-microglobulin to nephropathy. This study aims to determine if Beta-2-microglobulincan be added to the gold standards in indicating that there is a nephropathy during preeclampsia. This study was carried out using blood samples taken from preeclampsia patients in a secondary health facility in Edo state. E/U/Creatinine test was used to confirm elevation in the levels of urea and creatinine in the patients. Beta-2-microglobulintest was also carried out to see if the elevation in B2M level was significantly proportional to that of urea and creatinine

Fig. 1 shows the age groups of the study participants that were distributed into preeclamptic class, control class and PIH Group class. Out of a total of 124 preeclamptic respondents, 26% were within the 36-40 age category whereas 44% were within the 31-35 age category. Adding both together, it is easy to suggest that 70% of the 124preeclampsiapatients that were observed were within the age 31-40. In the positive control (fig. 1b), 61% of the respondents were also within the age 31-40. The PIH Group as well, presented a 60 % distribution for age 31-40.

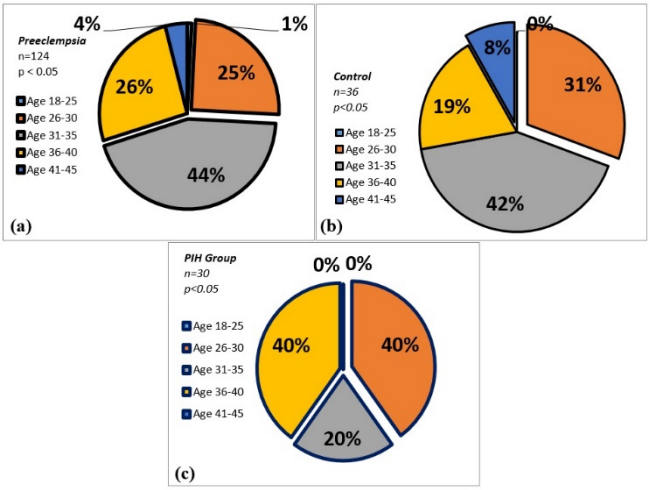

Fig 1. Age groups of (a) preeclampsia (b) control and (c) PIH Group respondents

Fig. 2 distributes the participants on the basis of their tribe. It is noticed that majority of the sufferers were Binis (53 out of 124). This is expected because the secondary health facility used in this study is located in Edo State and the majority ethnic group in this state is the Bini. The fact that Esans, Etsakos, Deltans and Ibos are also represented within the geographical area indicates that the health facility was accessed majorly by people within the catchment area of the hospital.

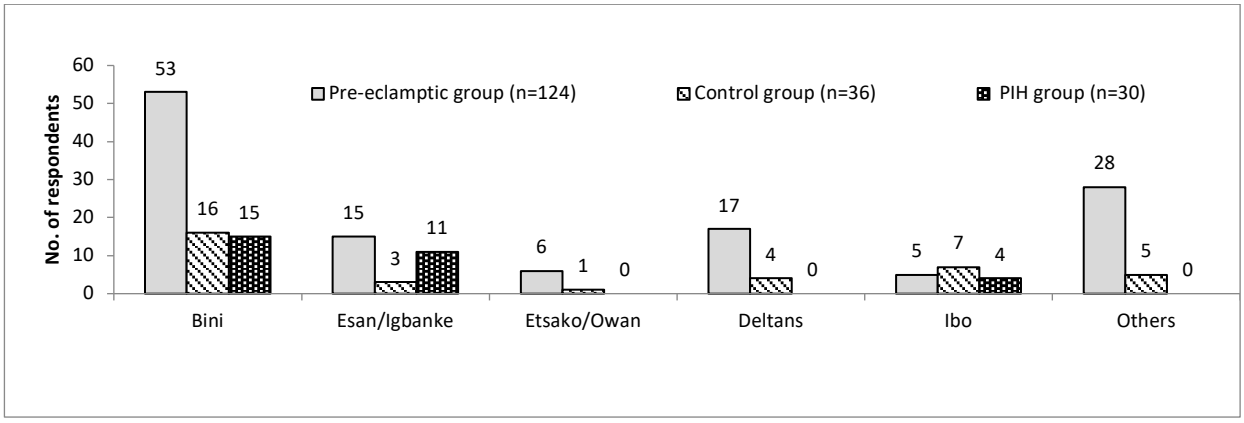

Fig. 2. Percentage distribution of respondents on the basis of tribe

Table 1 presents the demographic data of the respondents. It further distributes the respondents into marital status, educational status and employment status. It is noticed that 2.4% (3 out of 124) of the respondents were single mothers and 74.2% (92 out of 124) respondents were first married. Among the preeclampsia cases, the normal cases and the PIH Group, majority of the respondents were in their first marriage whereas, a smaller percentage were those who were remarried and single mothers. However, it can be noticed that a significant percentage of those who had preeclampsia were remarried when compared to the control (p-value<0.05).

Table 1. Demographic data of respondents

Queries	Preeclampsia cases (A) n (%) (N=124)	Control (B) n (%) (N=36)	PIH Group(C) n (%) (N=30)	(A+B)	A+C)	(B+C)
				p-values		
Marital status						
-Single	3 (2.4)	2 (5.6)	0	0.323	0.032*	0.041*
-First Marriage	92 (74.2)	33 (91.7)	10 (100)	0.041	0.006*	0.032*
-Remarried	29 (23.4)	1 (2.8)	0	0.013	0.027	0.072
Educational status						
-None	4 (3.2)	0	0	0	0	0
-Primary	17 (13.7)	3 (8.3)	3 (30)	0.442	0.441	0.989
-Secondary	47 (37.9)	16 (44.5)	3 (30)	0.110	0.028*	0.001*
-Post-secondary	56 (45.2)	17 (47.2)	4 (40)	0.142	0.146	0.083
Job status						
-Employed	102 (82.3)	27 (97.5)	8 (80)	0.192	0.892	0.173
-Unemployed	22 (17.7)	9 (2.5)	2 (20)	0.014	0.070	0.009*
Job type						
-Business owner/Trader	86 (69.4)	26 (72.2)	9 (90)	0.211	0.045*	0.064
-Civil servant	16 (12.9)	5 (13.9)	0	0.791	0.001*	0.001*
House wife	22 (17.7)	5 (13.9)	1 (10)	0.075	0.051	0.103

**significant*

We also observed that the participants were majorly educated because at least 8% of the respondents, irrespective of the class, had a primary education. It is also observed that majority of the respondents were employed. For instance, in preeclampsia cases, 82% of them were employed compared to 17.7% that were unemployed and in the PIH Group, 80% were employed compared to the 20% that were unemployed.

Table 2 presents the analytes of respondents based on trimesters for the assessment of kidney function. Usually, it is expected that preeclampsia becomes significant at 2nd trimester which is why results were not observed from the 1st trimester. In the second trimester, a significant increase in the level of beta-2-microglobulin was observed when the preeclampsia class with a value of 1.836 pg/dl was compared against the PIH Group with a value of 0.761 pg/dl. Similarly, it was also observed that in the normotensive group with a B2M value of 1.696 pg/dl, there was a significant reduction in the PIH group with a B2M value of 0.761 pg/dl. These all translate to an increase in B2M levels in the 2nd trimester. In preeclampsia cases, plasma urea value was noted to be 24.479 pg/dl and when compared against the PIH Group, there was an elevation to 36.020 pg/dl. Usually, reduction in plasma urea levels is expected in preeclampsia. Thus, the reduction noted in this study already suggests preeclampsia.

Table 2. Analytes of respondents presented on the basis of trimesters for assessment of kidney function. Only means of replicates have been presented

Queries	Trimester	Preeclampsia cases (A) (n=62)	Control (B) (n=16)	PIH Group(C) (n=15)	(A+B)	(A+C)	(B+C)
					p-values		
B2 Microglobulins (pg/dl)	Second	1.836	0.761	1.696	0.000	0.406	0.005
	Third	1.747	0.447	2.111	0.000	0.057	0.002
Plasma Urea	Second	24.479	36.020	25.859	0.000	0.472	0.031
	Third	22.613	35.590	40.445	0.005	0.000	0.042
Plasma-Creatinine	Second	0.904	0.800	0.737	0.279	0.004	0.059
	Third	0.911	0.740	0.810	0.109	0.081	0.137

Elevation in creatinine levels indicates nephropathy. We observed that there was significant elevation in creatinine levels when the preeclampsia group (A) where the plasma creatinine value was 0.904 pg/dl compared to the normotensive group (B) where the plasma creatinine value was 0.737 pg/dl (p value of A+B <0.05 indicating significance).

It was also observed that in the third trimester, there was elevated B2M levels when the preeclampsia group was compared to the PIH Group. The general output in this study is that B2M elevation, plasma urea reduction and plasma creatinine elevation were reported for preeclampsia. Since creatinine is the gold standard, B2M increase might be suggestive of a nephropathy.

What was observed was that preeclampsia caused a significant increase in B2M levels, a reduction in plasma urea levels and an elevation in plasma creatinine levels (Table 3).

Table 3. Analytes of respondents presented on the basis of trimesters for assessment of kidney function. Only means of replicates have been presented

Queries	Preeclampsia cases (A) (µ±SEM) (n=124)	Control (B) (µ±SEM) (n=36)	PIH Group(C) (µ±SEM) (n=30)	(A+B)	(A+C)	(B+C)
				p-values		
B2 Microglobulins (pg/dl)	1.79±0.05	0.68±1.33	1.92±0.15	0.000	0.291	0.000
Plasma Urea	23.54±0.72	35.80±3.21	33.96±2.23	0.004	0.000	0.173
Plasma-Creatinine	0.90±0.19	0.76±0.64	0.79±0.31	0.00	0.013	0.182

Table 4 shows two types of preeclampsia based on severity – mild preeclampsia and severe preeclampsia. It was noted that as the severity of preeclampsia increased, the level of B2M also increased significantly. However, for plasma urea and plasma creatinine, although there was elevation in their levels, it was not significant.

Table 5 shows the analytic composition of preeclampsia subjects separated on the basis of BMI. This is because many studies have shown that BMI is a risk factor for preeclampsia and cardiovascular disorders. When the mean values for the normal was compared against that of the overweight, the p-value was greater than 0.05 so it was not significant. The same was observed when comparing the normal and the obese.

Table 4. Analyte composition of preeclamptic subjects separated on the basis of severity of disease

Analytes	Groups	N	Mean	Std. Error Mean	p-value
B2 Microglobulins (pg/ml)	Mild	39	1.5081	0.0619	<0.001
	Severe	84	1.9185	0.0652	
Plasma Urea (mg/dl)	Mild	39	23.28	1.5644	0.809
	Severe	84	23.661	0.7886	
Plasma-Creatinin (mg/dl)	Mild	39	0.8519	0.0384	0.067
	Severe	84	0.9283	0.0218	

Table 5. Comparing Analyte composition of preeclamptic subjects separated on the basis of BMI

	Group 1 – Normal vs Overweight					Group 2 – Normal vs Obese				
		N	Mean	SEM	p		N	Mean	SEM	p
Beta-2-microglobulins (pg/ml)	Normal	23	1.7553	0.132	0.835	Normal	23	1.7553	0.132	0.617
	Overweight	71	1.7842	0.066		Obese	30	1.8383	0.103	
Urea (mg/dl)	Normal	23	20.2235	2.237	0.061	Normal	23	20.224	2.237	0.051
	Overweight	71	23.9744	0.865		Obese	30	25.082	1.258	
Creatinine (mg/dl)	Normal	23	0.8967	0.058	0.609	Normal	23	0.8967	0.058	0.810
	Overweight	71	0.9236	0.023		Obese	30	0.88	0.041	

4. Discussion

Preeclampsia is a frequent cause of increased proteinuria in pregnancy. It is characterized as pregnancy-induced hypertension and proteinuria, and it affects 2%–8% of pregnancies (8). Proteinuria was recently eliminated by the American College of Obstetricians and Gynecologists as a requirement for the diagnosis of preeclampsia in 2013 (9). So it's feasible that 10% of women in recent trials with clinical and/or histological preeclampsia symptoms didn't have proteinuria (10). A hypothesis however, that preeclampsia could be caused by a decrease in uteroplacental perfusion, which causes uteroplacental ischemia has been made in several studies (1).

In medicine, the gold standard for determining renal anomalies is the urea and creatinine test. Preeclampsia patients have creatinine and urea levels similar to non-pregnant women instead of normal pregnant women. In normal pregnant women, the globular filtration rate increases with a significant renal insufficiency in the serum creatinine. Studies though, have begun to link Beta-2-microglobulin to nephropathy. This study aims to determine if B2M can be added to the gold standards in indicating that there is a nephropathy in preeclampsia. It is suspected that if one more parameter is added to the existing gold standards for determining the occurrence of nephropathy, it could increase the confidence level of nephrologists.

The results demonstrate a significant increase of Beta-2-microglobulin levels gotten from the preeclampsia patients as well as a reduction in the globular filtration rate and renal plasma flow due to risks factors such as age, marital status and educational status. This is an indication of suggestive nephropathy and is only confirmed by the elevation of creatinine levels. Based on the age groups, it can be noted that majority of the preeclamptic patients were within the ages 31-40. According to demographics, this age bracket is regarded as the productive age for humans. This suggests that women within this age bracket are more susceptible to developing preeclampsia during pregnancy.

Upon observation of the preeclampsia cases, normal (normotensive) control and PIH Group, majority of the respondents were in their first marriage and a smaller percentage, were those who remarried. However, a significant percentage of those who remarried have an occurrence of preeclampsia when compared to the control with p value < 0.03. This observation has shown that remarriage may be a possible risk factor of preeclampsia. On the basis of educational status, a very large number of the respondents were educated with having at least a primary education irrespective of the class. Upon comparison of the preeclampsia cases and the control, it is observed that there is no association between educational status and preeclampsia and no significant changes. Majority of the respondents were employed in the preeclampsia cases, normal control and PIH Group with no significant changes. Hence in this study, there is no evidence that employment status is a risk factor for preeclampsia.

In this study, the level of B2M elevated significantly in the second and third trimesters with a percentage increase of 163.23%. The level of plasma creatinine also increased significantly with a percentage increase of 18.4% while the level of plasma urea dropped significantly with a percentage decrease of 34.25%. Though not proportional, the elevation in the levels of B2M with that of plasma creatinine might support the fact that B2M could be used in indicating nephropathy in preeclamptic women.

This study reports two types of preeclampsia based on severity – mild preeclampsia and severe preeclampsia. Among the participants, B2M levels were significantly higher in patients with severe preeclampsia than in those with mild preeclampsia. The elevated B2M levels can be linked to glomerular dysfunction as severe preeclampsia can be

characterized by decreased urine output and fluid retention (edema), symptoms not typically found in mild preeclampsia. The levels of plasma urea and plasma creatinine also increased, though insignificantly (p-value > 0.05). This might suggest that the levels of plasma urea and plasma creatinine are not as sensitive as that of Beta-2-microglobulin and so are not particularly effective in indicating the severity of preeclampsia in diagnosed patients.

This study also attempts to link the analyte composition of preeclamptic subjects to their BMI (Table 5). Earlier studies on this have reported that BMI is a risk factor of preeclampsia. A study in the USA reported that an elevated risk of preeclampsia is strongly correlated with increasing BMI (11). Another study by Jeyabalan (12). showed that the total likelihood of preeclampsia is roughly two to three times higher in people who are obese. Even within the normal range, preeclampsia risk increases gradually with rising BMI (12). Studies carried out to evaluate the influence of BMI on glomerular filtration (13), urea and creatinine levels (14, 15) and serum B2-Microglobulin (3) also showed that BMI was a determining factor for each of these subjects. However, in this study, BMI does not seem to have any correlation with preeclampsia as the increase in analyte composition of the preeclamptic subjects when comparing normal with overweight and normal with obese was not significant (p-value > 0.05). This could be due to the fact that majority of the subjects were employed (about 82%) as studies have shown that increased physical activity counteracts the negative effects of BMI on kidney function by burning off extra calories that could induce stress on the kidneys.

While the correlation between an increase in B2M levels and preeclampsia displays potential, more investigation is necessary to fully comprehend its significance. To confirm the clinical usefulness of B2M levels as a biomarker for preeclampsia, studies with larger participant pools are required. Furthermore, as with any diagnostic aid or biomarker, it is vital to establish B2M's specificity, sensitivity, and predictive value (16-18).

This study found a considerable rise in beta-2-microglobulin levels. Beta-2-microglobulin is a protein that is important in the immune system and is frequently utilised as a biomarker for a variety of disorders. Its use as a potential signal for preeclampsia, a dangerous illness that affects pregnant women, is crucial. Preeclampsia is characterised by elevated blood pressure and organ damage, particularly to the liver and kidneys. It puts both the mother and the baby at risk, including early birth and even death. Understanding the underlying processes of preeclampsia is critical for early identification and effective treatment. This work sheds light on the involvement of B2M in the development of preeclampsia. In this study, elevated B2M levels were linked to preeclampsia. Understanding the link between B2M levels and preeclampsia may potentially lead to new therapeutic options. If high B2M levels are associated to preeclampsia, targeting this protein might be a feasible therapeutic strategy. We can eventually improve outcomes for pregnant women suffering by this deadly illness by identifying biomarkers and studying therapeutic alternatives.

Ethical Statement

Ethical approval of the ethical committee (Protocol. No. ADM/E.22/A/VOL.VII/1469.), was also obtained from the University of Benin Teaching Hospital.

Conflict of interest

None to declare.

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None to declare.

Authors' contributions

Concept: K.A., E.O.O, Design: K.A., E.O.O., Data Collection or Processing: K.A., E.O.O., Analysis or Interpretation: K.A., Literature Search: K.A., E.O.O., Writing: K.A.

References

1. Müller-Deile J, Schiffer M. Preeclampsia from a renal point of view: Insides into disease models biomarkers and therapy. World J Nephrol 2014; 3(4): 169-181. https://doi.org/10.5527/wjn.v3.i4.169
2. Moran P, Baylis PH, Lindheimer MD, Davison JM. Glomerular ultrafiltration in normal and preeclamptic pregnancy. Journal of the American Society of Nephrology, 2003;14(3) 648-652. https://doi.org/10.1097/01.asn.0000051724.66235.e0.
3. Maruyama Y, Nakayama M, Abe M, Yokoo T, Minakuchi J, Nitta K. Association between serum β2-microglobulin and mortality in Japanese peritoneal dialysis patients: A cohort study. PLoS ONE, 2022; 17(4): e0266882. https://doi.org/10.1371/journal.pone.0266882
4. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016 Jul 6;11(7):e0158765. doi: 10.1371/journal.pone.0158765.
5. Hladunewich MA, Derby GC. Renal disorders in pregnancy. In Brenner Rector's The Kidney. Elsevier, 2016; pp 2065-2085
6. Pacarizi H, Begolli L, Lulaj S, Gafurri Z. Blood Urea Nitrogen/Creatinine index is a Predictor of Prerenal Damage in Preeclampsia. J Health Sci, 2012; 2 61-65.
7. Lequin RM. Enzyme immunoassay (EIA)/enzyme-linked immunosorbent assay (ELISA). Clin. Chem., 2005; 51(12):2415 - 2418.
8. Roccella EJ. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000; 183(1) s1–s22. https://doi.org/10.1067/mob.2000.107928
9. August P, Sibia BM. Preeclampsia: Clinical Features and Diagnosis. Uptodate.com. https://www.uptodate.com/contents/preeclampsia-clinical-features-and-diagnosis/[Accessed: 23 June 2023]; 2023

10. Thornton C, Makris A, Ogle R, Tooher J, Hennessy A. Role of proteinuria in defining pre-eclampsia: Clinical outcomes for women and babies. Clin Exp Pharmacol Physiol, 2010; 37(4) 466–470. https://doi.org/10.1111/j.1440-1681.2009.05334.x

11. Olson KN, Redman LM, Sones JL. Obesity "complements" preeclampsia. Physiological Genomics, 2019; 51(3): 73-76. Doi: 10.1152/physiolgenomics. 00102.2018

12. Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. Nutr Rev, 2013; 71(1): S18-S25. Doi:10.1111/nure.12055

13. Gerchman F, Tong J, Utzschneider K. M, Zraika S, Udayasankar J, McNeely M. J et al. Body Mass Index is Associated with Increased Creatinine Clearance by a Mechanism Independent of Body Fat Distribution. J Clin Endocrinol Metab, 2009; 94(10): 3781–3788.

14. Ude UA, Kalu ME, Ogbonna CL, Usanga VU, Azi SO. Evaluation of urea creatinine levels and proteinuria among obese individuals within Abakaliki metropolis. Niger J Basic Clin Sci., 2022; 19:120-125.

15. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, Vogelvang TE, Lely AT, Franx A, et al. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. BJOG. 2018 Dec;125(13):1642-1654. doi: 10.1111/1471-0528.15394.

16. Huppertz B, Kingdom J. Can placental pathology explain the progression from pre-eclampsia to HELLP syndrome? Acta Obstetricia et Gynecologica Scandinavica 2004; 83(10) 1085-1090.

17. Roberts JM, August PA. Preeclampsia: pathogenesis diagnosis and management. JAMA, 2019; 322(6) 579-586.

18. Roberts JM, Hubel CA. The two-stage model of preeclampsia: variations on the theme. Placenta, 1999; 20: S32-S37.