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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Original Research Article

The role of salivary uric acid as predictive marker for preeclampsia in comparison with serum uric acid

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Abstract

Background: Pregnancy may be complicated by many medical disease which convert the pregnancy to high risk one, many effort try to decrease the complication by early detection once, and by safe non invasive test another.
Aim & Objective: To evaluate the role of salivary uric acid in PET versus normal pregnancy in comparison with serum uric acid.
Materials and Methods: The study involved 180 patient divided into three group 60 patient healthy not pregnant women as control, 1st study group (A) 60 normotensive pregnant women in third trimester, 2nd study group (B) 60 patient diagnosed as PET both group in their third trimester of pregnancy, uric acid levels in both the serum & saliva was recorded by ELISA and the result was compared statistically. A cross-sectional study performed at AlYarmouk Teaching Hospital from October 2022 to October 2023.
Result: The result show when compare serum and salivary uric acid level in the three studying groups the mean of serum uric acid level were46.65±6.76mg/dl, 50.03±6.28mg/dl, 63.31±3.61 mg/dl in the non pregnant,pregnant,pregnant with PET consequently with obvious difference P-value 0.0001. Salivary uric acid was significantly increased in the pregnant PET group mean level was (50.59-83.58mg/dl) in comparison with (33.95-63.11mg/dl)in non pregnant and (38.94-66.93mg/dl) in pregnant group were the p- value 0.0001
Conclusion: Salivary UA can be used as a simple non invasive test to monitor women with preeclampsia.

Keywords: Salivary uric acid, Preeclampsia, Serum uric acid.

Received: 31-08-2024; **Accepted:** 25-10-2024; **Available Online**: 13-08-2025

1. Introduction

Preeclampsia considered a gestational hypertension with proteinuria (either 300 mg/24 hours or ≥ 30mg/dL (≥1+ on dipstick) in form of about two urine samples taken 6 hours between each, no more than 7 days apart.[1] Preeclampsia, hypertensive disorder and multisystem disease which complicated in 2% to 8% of nulliparous pregnancies, 14% in twining, 18% in previous preeclampsia.[2]

Preeclampsia classified into mild form (where Blood pressure usually shown ≥ 140/90 taken twice with 6 hours interval between each reading with associated Protein in urine ≥ 300mg/24hr or ≥ 1 + on 2 urine samples 6 hours apart, or severe form (where Blood Pressure usually shown ≥ 160/110 taken twice with 6 hours interval between each reading with associated Protein in urine ≥ 5g/24hr or ≥ 3+ on 2 urine samples 6hours apart, important findings that can be or not be part of the presentation like proteinuria, signs of organ impairment, such as decrease platelets count, hepatic function impairment, epigastric and right hypochondrial persistent sever pain, recently onset headache not responding to treatment, pulmonary edema, or renal impairment.[3]

Preeclampsia Pathogenesis is not fully understood still researches done to make a progress in this dilemma in the last decades. The placenta plays the major role in the pathogenesis of preeclampsia.[4] Thus, the model of two-stage was appear: partial remodeling of spiral artery in the uterus that leads to ischemia in placental tissue (stage 1) and the release of anti angiogenic factors from this tissue into the

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https://doi.org/10.18231/j.ijogr.v.12.i.3.9

maternal circulation that leads to damage of endothelium (stage 2).[5] These hypothesis may explain the hyperuricemia in early pregnancy with preeclampsia which precede hypertension and proteinuria.[6]

Uric acid is a terminal degeneration produce by catalyzing of purine by the xanthine dehydrogenase/xanthine oxidase (XDH/XO) enzyme, and contributes to the blood and saliva. XDH is change to its oxidase form XO by many factors including ischemia. Metabolism of Purine by XO couples the production of uric acid and the release of the superoxide (O2) free radical and is implicated as a contributor to oxidative stress. XDH/XO is present in various tissue but mainly in the gut and liver and increases following ischemic tissue damage.[7] Many studies revealed that uric acid may act as pro-inflammatory and pro-oxidant agent.

2. Material and Methods

Cross sectional study done in obstetric department in alyarmouk teaching hospital from October 2022 to October 2023after approval from Scientific- Ethical Committee of almustansiriyah university college of medicine patients included were 180 divided into three groups, first group: 60 non pregnant healthy women; second group 60 pregnant women beyond 20 weeks of pregnancy and third group involved 60 pregnant women diagnosed as PET according the criteria set by FIGO, ISSHP and USPTF as the following:

The presence of gestational hypertension in addition to any of the below newly occurring condition or may be two the findings ≥ 20 week of pregnancy:

1. Protein in urine: the presence of any of the following: Protein; Creatinine ratio; ≥ 30 mg/ml or ≥ 300 mg/24 hour ≥ +2 dipstick.
2. Dysfunctions of mother organs as:
   Sever injury to the kidney includes elevation in serum creatinine level ≥ 90 μmol/L or ≥ 1 mg/dL
   Liver involvement includes elevation in ALT and AST >40 IU/L and may have associated pain in right upper quadrant of the abdomen or in the epigastric region; Complications in the central nervous system as: blindness, persistent visual scotomata, altered mental status, clonus and severe headaches.
   Hematological complications: hemolysis, thrombocytopenia (platelet count <150000/μL) and DIC.
3. Placental -Utero impairment: like Stillbirth, umbilical artery Doppler waveform analysis Abnormality, Fetal growth restriction.

Detailed history was taken from patients with confirmation of gestational age by early ultrasound, examination was done all patients (general, vital signs, regional), investigation was send for them to confirm PET inclusion criteria pregnant patient healthy in the second trimester singleton, patient diagnosed PET in the second trimester, healthy women; exclusion criteria fetal distress, eclampsia, patient with any GIT problem, cardiovascular disease. Verbal consent was taken from the women enrolled in our study, Saliva and blood sample was taken from all patients and uric acid level was measured by ELISA

3. Result

Cross sectional study done in obstetric department in alyarmouk teaching hospital, patients included were 180 divided into three groups, first group: 60 non pregnant healthy women; second group 60 pregnant women beyond 20 weeks of pregnancy and third group involved 60 pregnant women, **Table 1** show demographic charesteristic feature of the studying groups.

Table 2 compare the level of serum and salivary uric acid in the three studying groups it show that the mean level of serum uric acid were 46.65±6.76mg/dl, 50.03±6.28mg/dl, 63.31±3.61 mg/dl in the non pregnant, pregnant, pregnant with PET consequently with difference significantly P-value 0.0001. Salivary uric acid was significantly increased in the pregnant PET group mean level was (50.59-83.58mg/dl) in comparison with (33.95-63.11mg/dl)in non pregnant and (38.94-66.93mg/dl) in pregnant group were the p- value 0.0001.

Table 3 show there is no significant difference regarding the age, gestational age, gravid, parity between the three studying groups but statistically significant difference regarding the level of serum uric acid and salivary uric acid between the groups as the P-value was 0.0001 as it shown also in **Table 4**.

Table 1: The demographic criteria of three study groups

		PET		Pregnant		Non-pregnant		p-value
		No	%	No	%	No	%	
Age (years)	<20	5	8.3	6	10.0	2	3.3	0.857
	20---24	18	30.0	14	23.3	18	30.0	
	25---29	10	16.7	14	23.3	14	23.3	
	30---34	13	21.7	14	23.3	15	25.0	
	=>35	14	23.3	12	20.0	11	18.3	
	Mean±SD (Range)	28.4±7.1(16-44)		28.2±64(16-43)		28.4±6.3(17-44)		0.981

Table 1 Continued…								
GA (weeks)	28---31	4	6.7	21	35.0	-	-	0.001*
	32---36	37	61.7	28	46.7	-	-	
	37---41	19	31.7	11	18.3	-	-	
	Mean±SD (Range)	35.1±2.2(29-39)		33.3±3.4(28-41)		-		0.001#
Gravida	Gravida 1	16	26.7	9	15.0	-	-	0.393
	2	8	13.3	8	13.3	-	-	
	3	10	16.7	14	23.3	-	-	
	4	11	18.3	8	13.3	-	-	
	5++	15	25.0	21	35.0	-	-	
	Mean±SD (Range)	3.3±2.1(1-8)		3.8±2.2(1-11)		-		0.181
Parity	Primi	17	28.3	12	20.0	10	16.7	0.680
	Para 1	9	15.0	9	15.0	10	16.7	
	2	14	23.3	19	31.7	13	21.7	
	3	8	13.3	10	16.7	10	16.7	
	4++	12	20.0	10	16.7	17	28.3	
	Mean±SD(Range)	2.0±1.9(0-7)		2.1±1.6(0-6)		2.5±2.0(0-8)		0.231
*Significant difference between percentages using Pearson Chi-square test (χ2-test) at 0.05 level.								
#Significant difference between two independent means using Students-t-test at 0.05 level.								
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.								

Table 2: The comparison of the levels of serum and salivary uric acid in three studying groups

		PET		**Pregnant**		**Non-pregnant**		**p-value**
		No	%	No	%	No	%	
Serum Uric Acid (mg/dL)	<40mg/dL	-	-	5	8.3	10	16.7	0.0001*
	40---49	-	-	21	35.0	28	46.7	
	50---59	8	13.3	32	53.3	20	33.3	
	60---69	50	83.3	2	3.3	2	3.3	
	70---79	2	3.3	-	-	-	-	
	=>80mg/dL	-	-	-	-	-	-	
	Mean±SD (Range)	63.31±3.61 (56.66-70.56)		50.03±6.28 (33.93-60.39)		46.65±6.76 (32.39-60.96)		0.0001^
Salivary Uric Acid (mg/dL)	<40mg/dL	-	-	4	6.7	6	10.0	0.0001*
	40---49	-	-	8	13.3	25	41.7	
	50---59	1	1.7	27	45.0	21	35.0	
	60---69	12	20.0	21	35.0	8	13.3	
	70---79	37	61.7	-	-	-	-	
	=>80mg/dL	10	16.7	-	-	-	-	
	Mean±SD (Range)	73.32±6.12 (50.59-83.58)		55.43±7.75 (38.94-66.93)		49.07±7.39 (33.95-63.11)		0.0001^
*Significant difference between percentages using Pearson Chi-square test (χ2-test) at 0.05 level.								
#Significant difference between two independent means using Students-t-test at 0.05 level.								
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.								

Table 3: The comparison between three studying groups regarding their characteristic features

	PET	Pregnant	Non-pregnant	P value
Age (years)	28.4±7.1 (16-44)	28.2±6.4 (16-43)	28.4±6.3 (17-44)	0.981
GA (weeks)	35.1±2.2 (29-39)	33.3±3.4 (28-41)	-	0.001#
Gravida	3.3±2.1 (1-8)	3.8±2.2 (1-11)	-	0.181
Parity	2.0±1.9 (0-7)	2.1±1.6 (0-6)	2.5±2.0 (0-8)	0.231
SBP (mmHg)	155.4±9.7 (140-170)	-	-	-
DBP (mmHg)	101.8±8.4 (90-120)	-	-	-
Serum Uric Acid (mg/dL)	63.31±3.61 (56.66-70.56)	50.03±6.28 (33.93-60.39)	46.65±6.76 (32.39-60.96)	0.0001^
Salivary Uric Acid (mg/dL)	73.32±6.12 (50.59-83.58)	55.43±7.75 (38.94-66.93)	49.07±7.39 (33.95-63.11)	0.0001^
#Significant difference between two independent means using Students-t-test at 0.05 level.				
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.				

Table 4: Comparison of P-value in pregnant PET group with non pregnant, pregnant non PET group regarding serum versus salivary uric acid level

	PET	Pregnant	Non-pregnant
Serum Uric Acid (mg/dL)	63.31±3.61 (56.66-70.56)	50.03±6.28 (33.93-60.39)	46.65±6.76 (32.39-60.96)
P value compared to Non-pregnant	0.0001#	0.005#	-
P value compared to pregnant	0.0001#	-	-
P value comparing All	0.0001^		
Salivary Uric Acid (mg/dL)	73.32±6.12 (50.59-83.58)	55.43±7.75 (38.94-66.93)	49.07±7.39 (33.95-63.11)
P value compared to Non-pregnant	0.0001#	0.0001#	-
P value compared to pregnant	0.0001#	-	-
P value comparing All	0.0001^		
#Significant difference between two independent means using Students-t-test at 0.05 level.			
^Significant difference among more than two independent means using ANOVA-test at 0.05 level. The mean level of serum uric acid was 63.31 mg/dL while salivary uric acid was 73.32 mg/dL in PET group, while the level was lower in pregnant non PET group which was 50.03, 55.43 mg/Dl respectively. The mean level of serum and salivary uric acid had the lowest level if compare with other studying groups			

Salivary uric acid test was sensitive and specific test as it shown in **Table 5**.

Table 5: Sensitivity and specifity of serum versus salivary uric acid test

Test Result Variables	Positive if Greater than or Equal To;	Sensitivity	Specificity
Serum Uric Acid (mg/dL)	56.5500	100	90.8
	57.9500	**93.3**	**92.5**
	60.9700	66.7	100
Salivary Uric Acid (mg/dL)	50.5750	100	46.7
	63.3850	**93.3**	**93.3**
	66.9400	86.7	100

4. Discussion

uric acid level in the serum was found to be about 25–35% in uncomplicated pregnancies due to blood volume expansion related to pregnancy, high renal blood flow, high glomerular filtration rate and lastly due to uricosuric action of estrogen.[8]

Serum uric acid concentrations continue to rise as pregnancy proceed till the end of pregnancy, as a result of the increased fetal production, its albumin binding level decreased and with associated decrease renal clearance.[9,10]

In pregnancies complicated by preeclampsia, the decreased in uric acid excretion level, will subsequently increase the level of serum uric acid.[11] Although uricemia usually followed by proteinuria.[12] In more recent studies shows increase in oxidative stress materials and reactive oxygen species the formation were all found to be another contributing resources for hyperuricemia observed in pregnant ladies complicated with preeclampsia.[13]

Due to the interaction between uric acid with proinflammatory cytokines, increased plasma levels of uric acid in pregnant women with preeclampsia may indicate a direct contribution for its pathophysiology as its role of action through promoting inflammation.[14]

Several studies as that made by Soukup et al[15] and Bahaa et al.[16] shows the presence of uric acid in saliva and discussed the equivocal relationship between serum and salivary uric acid levels and so sample from saliva may serve as a useful alternative marker than the invasive serum sample.

A study made by Soukup et al., found that uric acid taken from saliva regarded as a simple, non-invasive marker for patients with metabolic disorders with significant high level of salivary uric acid in patients had metabolic syndrome ($p = 0.002$).[15] In those without metabolic disorders, salivary uric acid level shown 184.9 ± 78.4 l (3.08 ± 1.3 mg/dl), while those with these disorders shown 278.1 ± 135.3 l (4.6 ± 2.2 mg/dl) where significances was shown between them.

In Bahaa et al. study showed that patients with renal failure in their end stages have stress markers of oxidation process in both the serum and saliva including the uric acid and malondialdehyde of which correlate well with our recent study. [16]

According to the study made by Sangeeta et al. showed that the cause of increase level of uric acid level in preeclampsia women is due to either a high production or low excretion of uric acid. [17]

Our findings were in the same results of other many studies as (Tejal et al. study[18] and Bainbridge et al. study[19]), where they agreed for the strong relation between increase in the mean values of serum uric acid and degree of toxemia and where uric acid level in the serum appears to be a selective marker in the evaluating the degree of preeclampsia. Our recent study, showed an equivocal relationship between serum uric acid level and salivary uric acid level, so uric acid level in saliva reflects what occur in serum, so suggest that it's level in the saliva act in the same way as uric acid in serum and so used to detect preeclampsia degree of severity.

In non-pregnant women, uric acid is known to have a relation with the cardiovascular disorder severity and may be cause for the conversion from pre-hypertension stat to hypertension condition in spite of no clear pathophysiology till now and so, placental pathology as well as maternal cardiovascular dysfunction might be reflected by salivary uric acid.

5. Conclusion

Salivary UA can be used as a simple non invasive test to monitor women with preeclampsia.

6. Ethical Approval

This study was approved by the Institutional Review Board of the local hospital (Al-Yarmouk Teaching Hospital), in accordance with the Declaration of Helsinki 2013; in addition, participated women received appropriate management by the researchers.

7. Funding Statement

The author received no specific funding for this article

8. Conflicts of Interest

The authors declare that they have no conflicts of interest.

9. Acknowledgments

The authors would like to express their deepest appreciation to all those who provided them the possibility to complete this article

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Cite this article: Ismael S, Hussein SS, Abdulqader MM. The role of salivary uric acid as predictive marker for preeclampsia in comparison with serum uric acid. *Indian J Obstet Gynecol Res*. 2025;12(3):409–414.