Uric Acid: Friend or Foe?

Azfar WS[a], Nor Azlin MI[b], Rizal AM[c], Othman H[a]

[a]Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Kuala Lumpur, Malaysia
[b]Department of Obsterics & Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Kuala Lumpur, Malaysia
[c]Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Kuala Lumpur, Malaysia

ABSTRACT

INTRODUCTION: Adverse pregnancy outcomes (APO) continue to trouble physicians worldwide, and uric acid has become a marker of interest in its prediction. Despite this, the correlation of uric acid in the third trimester is rarely studied, and the reference value for normal uric acid levels in pregnancy has yet to be established. This study was conducted to evaluate the association of uric acid levels in the third trimester of pregnancy and the development of APO, specifically gestational hypertension (GH), pre-eclampsia (PE), gestational diabetes mellitus (GDM), small for gestational age (SGA) and to determine the cut-off value of serum uric acid levels for screening of APO. **MATERIALS AND METHODS**: A retrospective observational study was conducted among 374 women who delivered at Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) and developed APO of interest and had serum uric acid levels taken during the third trimester of pregnancy. A cut-off value of 309μmol/L was used to assess the sensitivity and specificity in predicting APO. **RESULTS**: Associations were observed between 309 μmol/L and the development of GH (p<0.0005), PE (p<0.0005), GDM (p<0.0005), SGA (p=0.0264). Plotted ROC curves with a cut-off point of 309μmol/L demonstrated moderate predictive value of serum uric acid and the development of GH (AUC 0.639), PE (AUC 0.713), SGA (AUC 0.649), and low predictive value for GDM (AUC 0.4). **CONCLUSION**: Serum uric acid level of 309μmol/L in the third trimester of pregnancy is a moderate predictor of GH, PE, SGA and a poor predictor of GDM.

INTRODUCTION

Adverse pregnancy outcomes (APO) among mothers and foetus continue to challenge obstetricians and paediatricians worldwide. Among the APO include gestational hypertension (GH), pre-eclampsia (PE), gestational diabetes mellitus (GDM), and small for gestational age (SGA) babies. Recently serum uric acid levels have been highlighted to be associated with various APO. Studies have shown that elevated levels of uric acid have deleterious effects on the human body. Zhu et al.[1] found that high uric acid levels inhibit insulin signalling and directly cause insulin resistance, whilst Khosla et al.[2] demonstrated that high insulin levels could lead to endothelial dysfunction, causing decrease in nitric oxide production. This concurs with an animal study which stated that in animals, nitric oxide is needed for glucose uptake, hence its deficiency leads to hyperglycaemia.[3]

It is reported that hyperuricaemia plays an important role in abnormal placental implantation. High levels of uric acid induce endothelial dysfunction, inflammation & oxidative stress.[4] Endothelial dysfunction leads to decrease nitric oxide production. Low nitric oxide levels lead to dysregulation of trophoblastic invasion and inhibit the physiological transformation of spiral arteries, which can lead to PE.

Mador et al.[5] hypothesized that high uric acid levels in maternal circulation reflect its level in foetal circulation. The elevated uric acid levels in foetal circulation inhibit system A amino acid uptake and trigger endogenous signalling properties of uric acid in foetal tissue, hence suppression of growth rate. They also postulated that uric acid reacts directly with endothelial nitric oxide, thereby

depleting it and leading to endothelial dysfunction, PE, and eclampsia.

With regards to the reference interval of uric acid levels in pregnancy, no consensus has been agreed upon on the values, however there were efforts made by some studies to establish the reference intervals between the different trimesters. Greer et al. [6] managed to tabulate reference intervals for various analytes between the different trimesters which included uric acid levels whereby the first trimester ranged from 119-250μmol/L, second trimester from 143-292μmol/L and the third trimester from 184-375μmol/L. Yuhua Gao et al.[7] managed to establish trimesteric reference intervals for uric acid by non-parametric methods at their centre where the first trimester values ranged from 122-297μmol/L, second trimester from 129-327μmol/L and the third trimester from 147-376μmol/L.

In normal pregnancy, serum uric acid levels are expected to reduce by 25-30% during early pregnancy and increase as pregnancy progresses before decreasing to pre-pregnancy levels as the end of pregnancy approaches.[8] Altered renal handling has been proposed to be the cause for these pregnancy-linked changes. Many studies regarding serum uric acid levels in pregnancy and the development of APO mainly focused on the first and second trimester of pregnancy. To date, no consensus regarding standard reference intervals of uric acid in pregnancy has been agreed. Thus, this study investigated the association of uric acid levels in the third trimester of pregnancy and the development of APO, specifically GH, PE, GDM, SGA, and to determine a suitable cut-off value of serum uric acid levels for screening of the APO.

MATERIALS AND METHODS

This was a retrospective observational study conducted in Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM), a tertiary hospital in Kuala Lumpur, Malaysia, over three years. Recruitment into the study encompasses the inclusion criteria of all women who delivered at the hospital between 1st January 2016 and 31st December 2018, had serum uric acid levels measured during the third trimester, and developed at least one APO. Exclusion criteria were multiple gestation pregnancy, gouty arthritis disease, chronic kidney disease (CKD), Systemic Lupus Erythematosus (SLE), chronic hypertension, and post-dated deliveries. Patient details were obtained from the Integrated Laboratory Management System (ILMS) and in-house patient's medical record system (c-HETS). Individual case notes were reviewed for clinical progression and APO development. The predictive value of elevated serum uric acid levels in the third trimester and the development of APO (GH, PE, GDM, SGA) were assessed.

A cut-off value of 309μmol/L recommended based on a study by Bellomo et al.[9] was used to observe its sensitivity and specificity in developing APO among the study recruits. Primary outcome measures were APO (GH, PE, GDM, SGA). Secondary outcome measures were the uric acid cut-off value and the cut-off value's sensitivity and specificity. GH is defined as systolic blood pressure (SBP) of ≥140mmHg and/or diastolic blood pressure (DBP) of ≥90mmHg detected for the first time after 20 weeks of gestation.[10] PE is clinically diagnosed by the presence of *de novo* hypertension after 20 weeks of gestation with one or more of the following viz. significant proteinuria, renal insufficiency (serum creatinine ≥ 90μmol/L or oliguria), liver disease (raised transaminases or severe right upper quadrant pain or epigastric pain), neurological problems (altered mental status, hyperreflexia, severe headache), haematological disturbances (thrombocytopenia, coagulopathy), and foetal growth restriction.[10] GDM is defined as glucose intolerance of variable degree with onset or first recognition during pregnancy.[11] SGA is defined as infants with birth weight (BW) below the 10th percentile for gestational age.[12]

The sample size calculation for this clinical study was performed using the prevalence formula by Jingli et al.[13] as presented below. A total of 374 samples were finalized after factoring in a 20% possible dropout.

Serum uric acid was measured using the Uricase method by ARCHITECT c16000 analyzer (Abbott Diagnostics,

$$n = \frac{z^2 P(1 - P)}{d^2}$$

n = sample size
Z = Z statistic for a level of confidence (for level of confidence 95%, Z value is 1.96)
P = expected prevalence or proportion (in proportion of 1, if 20%, P = 0.02)
d = precision (in proportion of 1, if 5%, d = 0.05)

Abbott Laboratories, Illinois, United States) in our hospital chemical pathology laboratory with MS ISO 15189 accreditation.

Ethical statement

The study received approval from the UKM Research Ethics Committee (FF-2019-262)

Statistical analysis

Non-normally distributed continuous variables were expressed as median and interquartile range (IQR). Pearson's chi-square test of independence was used to assess the association of serum uric acid level cut-off point of 309μmol/L and the development of each APO of the study. Statistical significance was defined as p-value <0.05. Receiver Operating Characteristic (ROC) curve was plotted for each APO, and the area under the curve (AUC) was measured to investigate the value of elevated third-trimester serum uric acid levels and the development of APO (GH, PE, GDM, SGA). The cut-off point of 309μmol/L was also plotted on each ROC curve to assess the sensitivity and specificity. All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows Version 26.0 (IBM Corp., Armonk, NY)

RESULTS

A total of 374 women were recruited into the study. The demographics of the recruits are displayed in Table I. 75.0% of recruits had GH, 30.2% had PE, 42.2% had GDM, 9.1% had SGA babies. 61.8% had serum uric acid levels of ≥309μmol/L.

An association was observed between serum uric acid levels of ≥309μmol/L and the development of GH. Among recruits whose uric acid levels were ≥309μmol/L,

Table I: Demographic characteristics of participants whose uric acid levels were taken during the third trimester

Characteristics	n (%)
Age in years	32 (29-36)*
Parity	
Nulliparous	139 (37.2)
Multiparous	235 (62.8)
Ethnicity	
Malay	293 (78.3)
Chinese	44 (11.8)
Indian	11 (2.9)
Others	10 (2.7)
Foreigners	16 (4.3)
Gestation at which uric acid levels were taken	
28wks (<203 days)	10 (2.7)
29wks (<210 days)	20 (5.3)
30wks (<217 days)	10 (2.7)
31wks (<224 days)	11 (2.9)
32wks (<231 days)	14 (3.7)
33wks (<238 days)	23 (6.1)
34wks (<245 days)	19 (5.1)
35wks (<252 days)	24 (6.4)
36wks (<259 days)	37 (9.9)
37wks (<266 days)	76 (20.3)
38wks (<273 days)	71 (19.0)
39wks (<280 days)	53 (14.2)
40wks (280 days)	6 (1.6)
Gestational age at delivery	
<34 weeks	26 (6.9)
34 - <37weeks	79 (21.1)
37 – 40 weeks	269 (72.0)
Mode of delivery	
Spontaneous Vaginal Delivery (SVD)	189 (50.5)
Elective LSCS	22 (5.9)
Emergency LSCS	163 (43.6)
Adverse Pregnancy Outcomes (APO)	
Gestational Hypertension (GH)	281 (75.1)
Pre-eclampsia (PE)	113 (30.2)
Gestational Diabetes Mellitus (GDM)	158 (42.2)
Small for gestational age (SGA)	34 (9.1)
Number of APO	
Single APO	211 (56.4)
>1 APO	163 (43.6)

*IQR: Interquartile range

82.2% developed GH; of recruits whose uric acid levels were <309μmol/L, 63.6% developed GH ;(P< 0.0005), Table II. An association was also observed between uric acid levels of ≥309 μmol/L and the development of PE. Among recruits whose uric acid levels were ≥309 μmol/L, 39.4% developed PE, whereby those with uric acid levels <309 μmol/L, 15.4% developed PE; (P<0.0005), Table II. A similar observation was noted between uric acid levels of ≥309μmol/L and the development of GDM, whereby 34.6% developed GDM. For those recruits whose uric acid levels were <309μmol/L, 54.5%

developed GDM (P<0.0005), Table II. Association was also observed with small for gestational age (SGA) where 11.7% of recruits with serum uric acid levels ≥309μmol/L delivered SGA babies, and those with serum uric acid levels <309μmol/L, 4.9% had SGA babies. (P=0.0264), Table II.

Table II: Association between cut-off serum uric acid levels ≥309μmol/L and the development of studied APO among participants
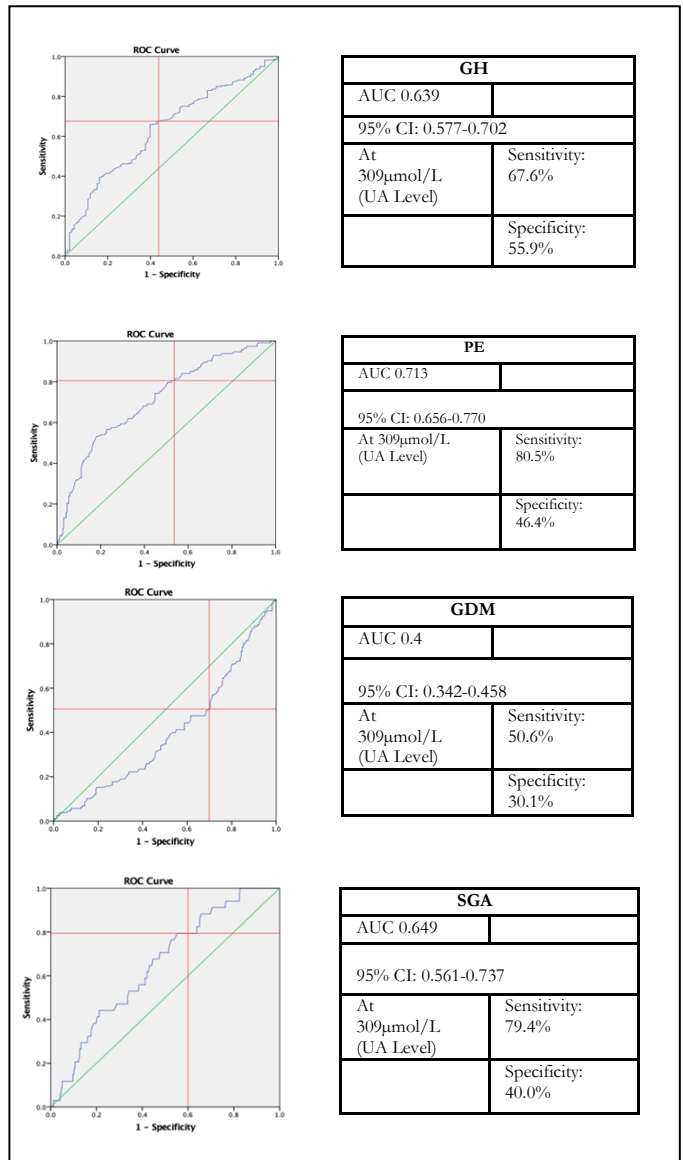
Adverse Pregnancy Outcomes	Uric Acid Values		Chi-square test of independence
	≥ 309μmol/L	< 309μmol/L	
Gestational Hypertension			
Yes	190	91	χ^2 (1, N = 374) = 16.38
No	41	52	p < 0.0005
Pre-eclampsia			
Yes	91	22	χ^2 (1, N = 374) = 24.15
No	140	121	p < 0.0005
Gestational Diabetes Mellitus			
Yes	80	78	χ^2 (1, N = 374) = 14.35
No	151	65	p < 0.0005
Small for Gestational Age			
Yes	27	7	χ^2 (1, N = 374) = 4.93
No	204	136	p = 0.0264

χ^2 = chi square value, N = sample size, p = p value

The plotted ROC curves demonstrate the moderate predictive value of third-trimester serum uric acid levels and the development of GH, PE, SGA, and low predictive value for GDM, Figure 1.

DISCUSSION

This study investigated the association between raised serum uric acid levels and the development of APO among pregnant women in the third trimester of pregnancy. We chose to study the third trimester as most studies focused on the first and second trimester, yet the third trimester is as equally important. By having a cut-off value in the third trimester, we would be able to identify pregnant women at risk of developing certain APO, especially among unregistered/unrecorded pregnancies presenting in the third trimester, which is quite significant, especially among foreigners from less developed countries.

GH	
AUC 0.639	
95% CI: 0.577-0.702	
At 309μmol/L (UA Level)	Sensitivity: 67.6%
	Specificity: 55.9%

PE	
AUC 0.713	
95% CI: 0.656-0.770	
At 309μmol/L (UA Level)	Sensitivity: 80.5%
	Specificity: 46.4%

GDM	
AUC 0.4	
95% CI: 0.342-0.458	
At 309μmol/L (UA Level)	Sensitivity: 50.6%
	Specificity: 30.1%

SGA	
AUC 0.649	
95% CI: 0.561-0.737	
At 309μmol/L (UA Level)	Sensitivity: 79.4%
	Specificity: 40.0%

ROC, Receiver Operating Characteristic; AUC, Area Under Curve; CI, Confidence Interval; GH, Gestational Hypertension; PE, Pre-eclampsia; GDM, Gestational Diabetes Mellitus; SGA, Small for Gestational Age

Figure 1: ROC curve and AUC for third-trimester serum uric acid in predicting GH, PE, GDM, SGA

We found that raised serum uric acid levels in the third trimester were an important indicator for developing GH, PE, and SGA but a poor indicator for GDM. Other studies have also demonstrated similar findings of raised uric acid levels and the development of APO; Niyonzima et al. [14] reported in a cross-sectional study conducted amongst 80 pregnant women in Rwanda of different gestations mean uric acid levels were 7.12mg/dL (423.5μmol/L) in the gestational hypertensive group compared to 4.49mg/dL (267.07μmol/L) in the non-hypertensive group. They concluded that the association of hypertension and hyperuricemia was recorded with a

strong correlation between blood pressure and serum uric acid levels. In another cross-sectional study, Lisnawati et al.[15] described that amongst 704 pregnant women in Indonesia whose serum uric acid levels were taken immediately before delivery revealed median serum uric levels of 4.9mg/dL (291.45µmol/L) among the gestational hypertension group, 5.18mg/dL (308.11µmol/L) among the pre-eclampsia without complications group and 7.6mg/dL (452.05µmol/L) among severe pre-eclampsia with organ involvement group. They concluded that maternal blood uric acid levels increased significantly, accompanying the severity of hypertensive disorders in pregnancy. Ugwuanyi et al.[16] described amongst 102 pregnant women with a period of gestation of more than 20 weeks revealed mean serum uric acid levels among the pre-eclamptic group to be higher at 6.08mg/dL (361.64µmol/L) compared the control group 5.2mg/dL (309.3µmol/L). They also found that women with elevated serum uric acid levels >6mg/dL (356.88µmol/L) were found to be four times more likely to have severe pre-eclampsia, 66 times more likely to deliver babies with APGAR score <7 in the first minute and three times more likely to deliver babies with lower birth weight than those with normal serum uric acid levels. It was concluded from their study that mean serum uric acid levels in a pre-eclamptic woman is higher than that of normal pregnant control, and higher levels are associated with severity of the disease and significantly associated with poorer perinatal outcome. In a cross-sectional study conducted in Nepal amongst 90 pregnant women between 24 to 36 weeks of gestation, mean serum uric acid levels were higher in the pregnancy-induced hypertension group compared to the control group; 5.46mg/dL (324.8µmol/L) versus 4.03mg/dL (239.7µmol/L)[17]. Ahmad et al.[18] reported that amongst 100 pregnant women who developed pre-eclampsia and serum uric acid was taken at mean gestational age of 33.5 weeks, had mean uric acid levels of 7.01mg/dL (417µmol/L). A meta-analysis on the prognostic role of serum uric acid in pre-eclampsia[19] included 196 studies involving 39540 women, found that higher uric acid was estimated for severe pre-eclampsia, eclampsia, haemolysis, elevated liver enzymes, and low platelet syndrome. They concluded that serum uric acid levels were increased in pre-eclampsia and can be used to predict disease severity and pregnancy complications. Akahori et al.[20] reported a mean serum uric acid value of 0.31mmol/L (310µmol/L) amongst pregnant women whose uric acid were taken before delivery (mean gestational age 36.3 weeks), delivered severe SGA babies. Zhaoet al.[21] studied 364 singleton pregnant women with initial presentation of gestational hypertension and found that a cut-off value of 303µmol/L moderately predicts the outcome of SGA babies. All these studies were in agreement with our findings. However, a systematic review and meta-analysis by Pecoraro et al.[22] concluded that after narrowing down to 21 studies involving more than 6000 women, no robust evidence currently exists to suggest that uric acid measurement is useful in predicting maternal and perinatal adverse outcomes.

As for the association between serum uric acid and GDM, there was less data than other APO. Yan Zhao et al.[23,] in their cohort study of 85609 pregnant Chinese ladies, found that the risk of GDM was significantly higher among pregnant women whose uric acid levels were between 203-412µmol/L and between 13-18 weeks of gestation. Rehman et al.[24] reported in their study of 172 pregnant women in the first trimester of pregnancy where mean uric acid levels of GDM mothers were higher compared to the control group; 3.73mg/dL (221.9µmol/L) vs. 3.19mg/dL (189.74µmol/L). Li et al.[25,] in their study of 1769 pregnant women, also reported that GDM group mothers had higher mean serum uric acid levels than non-GDM mothers (216.45µmol/L vs. 209.36µmol/L). They concluded that higher uric acid levels and a higher composite kidney function biomarker score during the 16-18th week of gestation were positively and independently associated with an increased risk of GDM. Ganta et al.[26,] in their prospective study of 312 pregnant women, found that the serum uric acid cut-off level of 3.5mg/dL (208.18µmol/L) had great sensitivity and specificity in predicting GDM when measured at 12 and 24 weeks of gestation. El-Gharib et al.[27], in their study of 250 women in the first trimester of pregnancy with elevated uric acid concentration > 4mg/dl (238µmol/L), 48.8% developed GDM. They recommended that serum uric acid measurement be done as a routine test during the first antenatal visit. Wolak et al.[28] also reported that elevated serum uric acid levels in the first 20 weeks of

pregnancy are associated with a higher risk for the development of GDM. Aparna[29] reported in her study of 225 women, a cut-off serum uric acid level of 3.4 mg/dL (202.23μmol/L) before 20 weeks of gestation was found to have a sensitivity of 90%, specificity of 95%, a positive predictive value of 50%, and a negative predictive value of 99% for the development of GDM. These studies demonstrated the association of uric acid as a marker for screening of GDM; however, they focussed mainly on the utility of uric acid during the first and second trimesters.

We used the cut-off value of 309μmol/L based on the study by Bellomo et al.[9] They demonstrated that amongst pregnant women with a mean time of presentation at 34 weeks (third trimester), elevated serum uric acid conferred an 8-to-9-fold risk for pre-eclampsia and a 1.6-to-1.7-fold risk for delivering small for gestational age babies and that the cut-off value also conferred excellent sensitivity, specificity, and likelihood ratios for diagnosis and prognosis. The cut-off value was lower than that suggested by Hawkins et al.[30] of 5.6mg/dL (333.1mmol/L), Ryu et al.[31] at 377.7μmol/L, Le et al.[32] at 393μmol/L and Goad et al.[33] at 417μmol/L (Table III). From our findings, the cut-off value of 309μmol/L gives moderate sensitivity and specificity for the development of APO. When we compared our findings with the study by Bellomo et al.,[9] our sensitivity for developing PE and SGA was high at 80.5% and 79.4%, but specificity was low at 46.4% and 40%, respectively. At the cut-off value of 309μmol/L, moderate sensitivity and specificity were seen for GH and low for GDM.

Table III: Sensitivity and specificity of uric acid cut-off values in relation to development of APO among participants

Uric Acid cut-off values	Gestational Hypertension (GH)		Pre-eclampsia (PE)		Gestational Diabetes Mellitus (GDM)		Small for Gestational Age (SGA)	
	Sen (%)	Spe (%)	Sen (%)	Spe (%)	Sen (%)	Spe (%)	Sen (%)	Spe (%)
309.0	**67.6%**	**55.9%**	**80.5%**	**46.4%**	**50.6%**	**30.1%**	**79.4%**	**40.0%**
333.1	51.6%	64.5%	67.3%	60.9%	39.9%	46.8%	67.6%	54.4%
377.7	31.7%	87.1%	50.4%	83.1%	19.6%	67.6%	44.1%	74.7%
393.0	27.0%	89.2%	43.4%	85.8%	17.7%	73.1%	41.2%	78.8%
417.0	19.2%	92.5%	31.9%	88.9%	12.7%	81.0%	29.4%	85.0%

Sen = Sensitivity, Spe = Specificity

At a cut-off value of 309 μmol/L, our findings demonstrated better sensitivity and specificity than the other studies' cut-off values, Table III. Although our sensitivity was good for PE and SGA, the specificity was relatively low. We postulated that factors like demographics of the study population, dietary habits, and lifestyle could have potentially affected the outcome, as shown in the study by Beydoun et al.[34] It could also indicate that uric acid as a sole marker for predicting APO might not be sufficient and requires additional supportive markers; however, as a screening marker, it confers excellent sensitivity.

The association between serum uric acid and GDM was not powerfully demonstrated in this study. We believed this could be due to the high prevalence of GDM in our population; hence a bigger sample size might be needed to assess the association of uric acid levels and the development of GDM.

The strength of this study lies with it being conducted amongst third-trimester pregnant women, where most studies had focused on pregnant women in the first trimester. Secondly, strict exclusion criteria were implemented to reduce the impact of confounding factors.

Limitation of the study includes being retrospective and being conducted at only one tertiary centre hence may not represent the country's population. Another limitation is that no consensus has been agreed upon regarding the specific gestation or days within the third-trimester uric acid should be taken. Apart from that, some pregnant women developed more than one APO, and the possibility of the results being affected by a combination of APO cannot be excluded. Regarding GDM, a higher sample size might be needed due to the high prevalence of GDM among pregnant women, which could give a different depiction.

Studies in the future should include a broader population with well-coordinated multicentric involvement and include agreed uric acid thresholds with certain gestational days or weeks in the third trimester to provide a more comprehensive and collective view of the research. We also believe that for future studies, more significant recruits should be incorporated and tailored to GDM as the sole APO could probably give a better insight into the utility of uric acid in the third trimester with GDM. As of current practice, uric acid is not typically taken to monitor the progress of GDM in pregnancy. We hope that in the future, it can be utilized for GDM monitoring as well.

CONCLUSION

This study demonstrated that serum uric acid levels in the third trimester of pregnancy, particularly at the cut-off point of 309μmol/L, is a moderate predictor of GH, PE, and SGA and a poor predictor of GDM. We also conclude that uric acid levels in the third trimester are as equally important as the levels in the first and second trimester of pregnancy. With this uric acid cut-off level, we hope that clinicians will have an early alert when an undocumented/unrecorded third-trimester pregnant patient arrives at the health facility.

DISCLOSURE

ACKNOWLEDGMENTS

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