ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.pharmascope.org/ijrps

Prediction of maternal diabetes and adverse neonatal outcome in normotensive pregnancy using serum uric acid

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Article History:

Received on: 06.07.2019
Revised on: 01.10.2019
Accepted on: 08.10.2019

Keywords:

Diabetes,
Foreseeing,
Small for gestational age,
Uric acid

ABSTRACT

Diabetes mellitus, with adverse neonatal events are challenging issues to all obstetricians and pediatricians, where uric acid could play a vital role. We aimed to assess the relationship and prognostic benefits of serum uric acid measured at about 20 weeks' gestation in normotensive pregnancy, with subsequent maternal diabetes, and neonatal complications. All singleton normotensive pregnant women with normal blood glucose, serum creatinine, and weight before pregnancy, whom attended Medical City Hospital, Department of Obstetrics and Gynecology in Baghdad, were involved and regarded as the case group, on the condition that their serum uric acid measured at 20 weeks' gestation > 3 mg/dl, but if $\leq$ 3 mg/dl, they would be registered as a control group. A complete follow up was performed regularly during pregnancy, and after delivery; regular assessments of maternal blood glucose were done up to one year. Maternal diabetes mellitus (DM), small for gestational age (SGA) neonates, and preterm delivery (PD) constituted (27.59%), (43.60%), and (1.97%), respectively in case group which had significantly included maternal DM and SGA (P <0.001). Also, elevated mid-pregnancy serum uric acid was strongly associated (P <0.0001) with maternal DM (5.86 $\pm$ 0.69) and SGA (4.78 $\pm$ 0.34). Cut-off values of uric acid of 4.76 mg/dl were best associated with maternal DM, while 4.33 mg/dl with SGA. In conclusion, the cut-off points of 4.76 and 4.33 mg/dl of maternal mid- normotensive pregnancy serum uric acid have the potential ability to predict Maternal DM and SGA, respectively.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v10i4.1736

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INTRODUCTION

It is well known that uric acid is linked to some pregnancy complications, such as hypertension and preeclampsia. Poor placental perfusion due to oxidative stress promoted by uric acid effects within the endothelial levels may be the major etiology (Singh *et al.*, 2019; Zhou *et al.*, 2018).

Humans, as well as great apes, seem to keep elevated serum uric acids. The reduced activity, which was followed by the silence of the uricase gene about 15 million years ago, could be the cause behind that, as the liver intracellular urates are naturally degraded by this gene (Johnson *et al.*, 2015; Kratzer *et al.*, 2014).

Insulin resistance and gestational diabetes are also involved with abnormal uric acid measurements. Serum uric acid levels usually become low in pregnancy, reaching 3 mg/dl (or even lower) during early pregnancy, caused by elevated estrogen levels with their uricosuric properties, and by the high blood flow to the kidneys. During the third

trimester, uric acid levels started to rise to touch 4-5 mg/dl near term (Johnson *et al.*, 1979).

Perinatal events are influenced by high maternal serum uric acid, including abnormal fetal growth, especially small for gestational age (SGA) and preterm delivery (PD). Hyperuricemia has a distinctive effect on the growth pattern of the neonates through an altered placental function. Fetal growth abnormalities are linked to higher perinatal morbidity and mortality rates (Gillon *et al.*, 2017; Jasim *et al.*, 2018).

Always it is better for the health care provider to predict complications rather than facing them emergently. This will allow a quicker step to managing patients in a safer way. The use of uric acid as a predictive tool to find out pregnancy outcomes and gestational diabetes is a recent approach (Damen *et al.*, 2016; Al-Momen *et al.*, 2018; Rezk *et al.*, 2018).

Metabolic syndrome in adults is associated with an increased prevalence of hyperuricemia, obesity, and insulin resistance, which may lead to diabetes mellitus (Bombelli *et al.*, 2018; King *et al.*, 2017).

Alcohol also is a risk factor for hyperuricemia, but in our community, it is prohibited for females in most of the instances (Makinouchi *et al.*, 2016; Moriyama, 2019; Al-Hemiery *et al.*, 2014).

The objectives of this study are to investigate the effects of normotensive pregnancy serum uric acid on later maternal diabetes and abnormal pregnancy outcomes. In addition to the potential ability of uric acid to predict the above parameters.

MATERIALS AND METHODS

Study design, data collection, and exclusion criteria

At Medical City Hospital, Department of Obstetrics and Gynecology, in Baghdad, the capital of Iraq, which is the main tertiary center that receives cases from all parts of the country.

Exclusion criteria

All visiting pregnant ladies during the second trimester ($\leq$ 20 weeks' gestational age) were involved on the condition that they were singleton with normal blood pressure (< 140/90 mmHg), blood sugar, and serum creatinine. Also, they were of normal weight before pregnancy (body mass index (BMI) should be less than 25) and a negative family history of diabetes mellitus. No chronic drug use, and no high- fat and/ or carbohydrate diet regularly during the study period. Any pregnant lady with anemia (hemoglobin $\leq$ 10 g/l), thrombocytopenia (platelet count < 150000/mm^3), positive dipstick of albumin in the urine (albuminuria), history of chronic illness such as hypertension or diabetes, and previous history of gestational diabetes was excluded. Also, any elevation in maternal blood pressure throughout gestation would be added to the exclusion criteria.

Serum uric acid was taken at around 20 weeks of gestation and measured by calorimetric assay (Sbin React 800; Spain). The Variance coefficient was 6%, according to the manufacturer.

All pregnant women whom outside exclusion criteria, with elevated serum uric acid levels > 3 mg/dl, were recruited in this study and considered as a case group. Normal serum uric acid before the third trimester during pregnancy is $\leq$ 3 mg/dl (Johnson *et al.*, 2015).

Involved pregnant ladies were followed up during regular hospital visits up to one year after delivery to assess their blood sugar. Women who failed to have regular checkups were excluded from the case group (added to the above exclusion points).

During an interval that started from 1st of December 2016 until the end of May 2018, the total number of recruited pregnant women was 406, and there was an extension of an extra 12 months' period of follow up for blood sugar measurements, which was ended in May 31, 2019. We recruited other 300 pregnant women as a control group during the same period, whom had the same inclusion criteria, but with non-elevated serum uric acid ($\leq$ 3 mg/dl) at 20 weeks of gestation.

Full history, examination, evaluation, gestational age assessment, management, and intervention were made by the attending obstetrician.

Definitions

Maternal diabetes mellitus (DM) was defined as a fasting blood glucose level of $\geq$ 7.0 mmol/l (WHO, 2006).

Small for gestational age (SGA), as an adverse neonatal outcome, was defined as a weight below the 10th percentile for the gestational age (Boghossian *et al.*, 2018).

Preterm babies were known when they were born before completed 37 weeks of gestation, while term neonates were defined as $\geq$ 37 gestational weeks at delivery (Jasim *et al.*, 2018; Al-Momen *et al.*, 2018).

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 22 (IBM Corp., Armonk, NY, USA), and *P*-value <0.001 was considered significant.

Table 1: Distribution of sub-groups

Sub-group	Case group, No (406)	Control group, No (300)	*P*- value
Maternal DM, No (%)	112 (27.59%)	10 (3.33%)	<0.001[a]
SGA, No (%)	177 (43.60%)	14 (4.67%)	<0.001[a]
PD, No (%)	19 (1.97%)	6 (2.00%)	0.056

a Chi−square test

Table 2: General patients' data specifications

Variable	Maternal DM (case vs[d] control)	*P*- value	SGA (case vs[d] control)	*P*- value	PD (case vs[d] control)	*P*- value
Maternal age, years (mean ± SD)	(23.1 ± 2.23 vs 22.8 ± 1.95)	0.364[a]	22.7 ± 1.67 vs 22.5 ± 1.53)	0.867[a]	22.8 ± 2.1 vs 22.3 ± 3.24)	0.723[a]
Weight rise during pregnancy, Kg	(14.83 ± 4.2 vs 14.94 ± 3.8)	0.762[a]	(9.81 ± 3.5 vs 9.89 ± 3.1)	0.847[a]	(9.60 ± 3.2 vs 9.81 ± 3.7)	0.283[a]
Parity, multigravida:primigravida	(36:76 vs 3:7)	0.267[c]	(58:119 vs 5:9)	0.418[c]	(3:5 vs 2:4)	0.095[c]
Mean blood pressure, mm Hg (mean ± SD)	(84.2 ± 7.9 vs 85.3 ± 6.4)	0.634a	(87.2 ± 8.7 vs 86.1 ± 6.9)	0.219[a]	(85.2 ± 5.1 vs 85.8 ± 4.8)	0.712[a]
Gestational age at serum uric acid sampling, weeks (mean ± SD)	(20.10 ± 2.2 vs 20.31 ± 2.5)	0.418[a]	(20.34 ± 3.1 vs 20.38 ± 2.7)	0.972[a]	(20.24 ± 2.6 vs 20.36 ± 2.3)	0.653[a]
Gestational age at birth, weeks (mean ± SD)	(38.21 ± 1.4 vs 37.96 ± 2.5)	0.283[a]	(38.10 ± 6.2 vs 37.32 ± 4.1)	0.176[a]	(36.82 ± 3.7 vs 36.14 ± 2.8)	0.291[a]
Neonatal sex, male: female	(55:57 vs 5:5)	0.814[c]	(90:87 vs 8:6)	0.008[c]	(5:3 vs 4:2)	0.013[c]
Birth weight, Kg (mean ± SD)	(4.15 ± 0.65 vs 4.08 ± 1.1)	0.321[a]	(2.11 ± 0.98 vs 2.32 ± 0.65)	0.093[a]	(2.03 ± 0.17 vs 2.11 ± 0.42)	0.216[a]
Admission to Neonatal Intensive Care Unit (NICU): n, %	(101, 90.18% vs 9, 90.00%)	0.978[b]	(128, 72.32% vs 10, 71.43%)	0.856[b]	(7, 87.50% vs 5, 83.33%)	0.925[b]

a Student t−test; b Chi−square test; c X^2 test; d Versus

Table 3: Mid-pregnancy serum uric acid in relation with maternal and neonatal conditions

Serum uric acid at mid-pregnancy	Case group: (SD ± mean)	Control group: (SD ± mean)	*P*-value
Maternal DM	5.86 ± 0.69	2.89 ± 1.46	<0.001
SGA	4.78 ± 0.34	2.63 ± 0.93	<0.001
PD	3.1 ± 0.16	2.97 ± 1.12	0.468

Table 4: Best computed values of mid-pregnancy serum uric acid using ROC curves

Serum uric acid for the variable (mg/dl)	Area under the curve	95% confidence interval	Cut-off limit of serum uric acid	Sensitivity (%)	Specificity (%)
Maternal DM	0.923	0.911-0.943	4.76	98.3	90.2
SGA	0.941	0.948-0.930	4.33	96.4	93.1

Data were expressed as means ± standard deviation (mean ± SD) for continuous variables, and the Student t-test was carried out for comparison. Gender and parity were analyzed with X^2 test, while related categorical variables were compared using the Chi-square test. Receiver operating characteristic (ROC) curve analysis was applied to determine the optimum level of a specific variable and to predict the values of the corresponding parameter.

Ethical statement

Institutional Review Boards of Al-Kindy College of Medicine and College of Medicine at the University of Baghdad had approved this research. Informed consent was obtained from all participants. Work was done in accordance with the Helsinki Declaration.

RESULTS AND DISCUSSION

General patients' characteristics

The total number (No) of involved pregnant women was 406 (case group). It appeared that 112 of them (27.59%) developed diabetes mellitus (DM) later on, either during gestation or up to one year after delivery. Small for gestational age neonates (SGA) were found in 177 cases (43.60%). Preterm delivery (PD) was found in eight neonates (1.97%). For the SGA subgroup, 22 babies (12.43%) had mothers with gestational diabetes mellitus up to one year after labor, while PD newborns had no one mother with diabetes. We included 300 pregnant women in the control group (with normal uric acid); maternal diabetes (up to one year after delivery) was found in ten cases (3.33%). SGA was seen in 14 neonates (4.67%). PD was noticed in six cases (2.00%). None of the mothers of SGA and PD neonates had diabetes during our observation. Maternal DM and SGA subgroups were significantly (P <0.001) seen in the case group when compared with controls, on the contrary of the PD subgroup. These findings are available in Table 1.

Correlation of different variables within subgroups

In Table 2; many variables were put in comparison between the same subgroups (either maternal DM, SGA, and PD) of different groups (cases and controls), such as mother's age, weight gain during pregnancy, neonatal birth weight, and admission to neonatal intensive care unit (NICU), and others. All characteristics in Table 2, unless indicated, were noted at 20 weeks of gestational age and failed to touch statistical significance (P > 0.001).

Association of maternal serum uric acid with each subgroup

Simple regression analysis was performed to find out if there is a relationship between mid-pregnancy maternal serum uric acid and specific neonatal complications, namely gestational age, and birth weight, as these outcomes are the most commonly reported events linked to maternal hyperuricemia in the literature as mentioned in the introduction above. We included a dichotomy pattern (positive versus negative) of the following complications; gestational age {preterm (positive) versus term (negative); 62 vs. 54, respectively}, and birth weight {<10^{th} percentile for the gestational age (positive) versus ≥ 10^{th} percentile for the gestational age (negative); 148 vs. 73, respectively}. Uric acid was significantly correlated with small for gestational age (SGA) babies using a t-test (P-value < 0.001). Also, mid-pregnancy serum uric acid was significantly correlated with maternal diabetes mellitus (up to one year after delivery) using a t-test (P < 0.001). All are illustrated in Table 3.

Cut-off values of mid-pregnancy serum uric acid that were associated with maternal diabetes and SGA are shown in Table 4.

Elevated serum uric acid is a strong risk factor for diabetes, and there is a relationship between serum uric acid during pregnancy, and small for gestational age (SGA) delivery (Dehghan *et al.*, 2008; Laughon *et al.*, 2009).

There are many studies that expressed the association between hyperuricemia and hypertension with/ or without pre-eclampsia in pregnant women (Shalal *et al.*, 2017; Khaliq *et al.*, 2018), where uric acid elevation lowers endothelial cell proliferation and migration, which may lead to endothelial damage, and abnormal placental and vascular development, and ultimately hypertension

with pre-eclampsia (Tangren *et al.*, 2018; Laughon *et al.*, 2011).

In this study, we tried something different through involving non- hypertensive pregnant ladies to assess the effects of serum uric acid (in mid-pregnancy period) on neonatal outcome and development of diabetes mellitus in these ladies (up to a year post-delivery). Moreover, we applied serum uric acid as an indicator to foresee the above-mentioned parameters.

We found a significant association between mid-pregnancy serum uric acid and maternal diabetes mellitus occurred later during pregnancy till one year after giving birth. This is inconsistent with another article that confirmed the relationship of maternal insulin resistance and uric acid (Laughon *et al.*, 2009). Other authors agreed with this concept in persons outside the pregnancy period (Modan *et al.*, 1987).

A cut-off value of mid-pregnancy serum uric acid of (4.76 mg/dl) was shown to predict maternal diabetes, either gestational or later, on up to one year after delivery. It is well-known that elevated serum uric acid levels predate diabetes mellitus appearance (type 2) in adults (non-pregnant), which may need several months to do so (Dehghan *et al.*, 2008). So that, we extended our monitoring of maternal blood sugar for a full one year after birth in order to have a better and more accurate assessment with such a follow-up time.

Up to our knowledge; this was not mentioned before except for a recent paper which used first trimester uric acid levels to predict gestational diabetes, without a follow up time (Ali *et al.*, 2019), and another publishing that stated a predictive value of uric acid of 5.94 $\pm$ 0.77 mg/dl for gestational diabetes only without extension after delivery, in both hypertensive and normotensive pregnancies (El-Ewa *et al.*, 2018), while herein this study; only pure normotensive pregnancies were involved, with a follow up time of one year after labor.

However, some authors considered uric acid alone is a weak predictor of gestational diabetes (Zhou *et al.*, 2012).

Regarding adverse neonatal outcome, increased serum uric acid was strongly associated with small for gestational age neonates (SGA), our findings were consistent with other researchers who suggested that a slightly abnormal renal function is related to serum uric acid, which in turn may lead to SGA in pregnant women with normal blood pressure (Zhou *et al.*, 2018; Akahori *et al.*, 2012).

Although insulin resistance that is associated with elevated uric acid levels during pregnancy is linked to excessive fetal growth; the resulted SGA neonates overcome due to exact unknown mechanism, this may indicate that fetal growth is affected by high concentrations of uric acid either directly or indirectly (Laughon *et al.*, 2011; Maged *et al.*, 2014). However, our data revealed that most of SGA cases came from non-diabetic mothers.

The cut-off limit of mid-pregnancy serum uric acid levels for the prediction of small for gestational age (SGA) was 4.33 mg/dl.

Again, based on our search, no comparative data was published before. Nevertheless; a fresh Korean study stated 6.35 mg/dl as a threshold of serum uric acid level that was related to SGA (Ryu *et al.*, 2019), and Indian scientists put down a serum uric acid level of 6.37 mg/dl to predict pregnancy outcomes (Nair and Savitha, 2017), while in Australia they found that abnormal perinatal events were associated with serum uric acid levels > 5.9 mg/dl (Hawkins *et al.*, 2012). All these values were taken during the third trimester of hypertensive pregnancies with/or without pre-eclampsia. In this paper, we included mid-pregnancy uric acid in normotensive women.

In general; high levels of uric acid are associated with and could predict maternal and neonatal adverse events (Hawkins *et al.*, 2012; Liu *et al.*, 2019), although some writers believed that uric acid measurements are bad prognostic parameters of maternal, and fetal outcomes in hypertensive pregnancies (Williams and Galerneau, 2002).

Preterm delivery was found in a small percentage of our babies whom mothers had high uric acid levels (1.97%) without reaching significance. Other articles that studied maternal hyperuricemia found a much higher occurrence and stronger relationship between maternal uric acid and prematurity (Nair and Savitha, 2017; Hawkins *et al.*, 2012). Such a difference may be explained by the fact that hyperuricemia is usually associated with hypertension and lead to some sort of placental damage (as written above), which in turn could be a possible cause of preterm delivery, while we recruited only normotensive pregnant ladies in this study (Tangren *et al.*, 2018; Laughon *et al.*, 2011).

This study has the power of a prospective approach having a large number of involved normotensive pregnant women, with 18 months of data collection, and another 12 months of maternal follow up. Also, we had the potential ability to predict maternal diabetes, and prognose adverse neonatal consequences using a simple test of serum uric acid, that is cheap and widely available in most of the settings,

even with limited resources. This may lead to fewer complications in both maternal and fetal or neonatal sides because the obstetrician and neonatologist will be well prepared to what have been already expected.

However; there are some limitations such as absence of kidney function assessments, and the possible high incidence of maternal diabetes and pregnancy outcome adverse events (SGA) within the studied sample, as it is usual for mothers in our part of the world not to strictly follow their obstetricians' instructions such as a healthy diet and lifestyle.

CONCLUSIONS

high serum uric acid levels at the middle of normotensive pregnancy are significantly related to late maternal diabetes (up to one year of follow up) and small for gestational age neonates. The value of uric acid (in mg/dl) $\geq$ 4.76 is used to predict maternal DM and $\geq$ 4.33 for SGA.

Acknowledgment

Authors would like to thank all the medical and paramedical staff at Medical City hospital for their great deal of support.

REFERENCES

Akahori, Y., Masuyama, H., Hiramatsu, Y. 2012. The Correlation of Maternal Uric Acid Concentration with Small-for-Gestational-Age Fetuses in Normotensive Pregnant Women. Gynecologic and Obstetric Investigation, 73(2):162–167.

Al-Hemiery, N., Dabbagh, R., Hashim, M. T., Al-Hasnawi, S., Abutiheen, A., Abdulghani, E. A., Rawson, R. A. 2014. Self-reported substance use in Iraq: findings from the Iraqi National Household Survey of Alcohol and Drug Use. Addiction, 112(8):1470–1479.

Al-Momen, H., Muhammed, M. K., Alshaheen, A. A. 2018. Neonatal Seizures in Iraq: Cause and Outcome. The Tohoku Journal of Experimental Medicine, 246(4):245–249.

Ali, O. A. S., Sawy, I. R., Salah, M. A., Kattaria, M. K. 2019. Predictive Value of First Trimester Uric Acid in Development of Gestational Diabetes. The Egyptian Journal of Hospital Medicine, 74(7):1675–1679.

Boghossian, N. S., Geraci, M., Edwards, E. M., Horbar, J. D. 2018. Morbidity and Mortality in Small for Gestational Age Infants at 22 to 29 Weeks' Gestation. Pediatrics, 141(2).

Bombelli, M., Quarti-Trevano, F., Tadic, M., Facchetti, R., Cuspidi, C., Mancia, G., Grassi, G. 2018. Uric acid and risk of new-onset metabolic syndrome, impaired fasting glucose, and diabetes mellitus in a general Italian population. Journal of Hypertension, 36(7):1492–1498.

Damen, J. A. A. G., Hooft, L., Schuit, E., Debray, T. P. A., Collins, G. S., Tzoulaki, I., Moons, K. G. M. 2016. Prediction models for cardiovascular disease risk in the general population: a systematic review. BMJ, 353.

Dehghan, A., Hoek, M. V., Sijbrands, E. J. G., Hofman, A., Witteman, J. C. M. 2008. High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes. Diabetes Care, 31(2):361–362.

El-Ewa, A., El-Berry, S. E. H., Salama, K., El-Maghraby, N. I. 2018. Lipids and uric acid in mid-second trimester and prediction of adverse pregnancy outcome. Benha Medical Journal, 35(2):145–145.

Gillon, T., Lüscher, B., Schneider, P., Marini, C., Surbek, D., Baumann, M. 2017. P 55 Role of uric acid and GLUT9 in pregnancy on neonatal development. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 9:61–61.

Hawkins, T. A., Roberts, J., Mangos, G., Davis, G., Roberts, L., Brown, M. 2012. Plasma uric acid remains a marker of poor outcome in hypertensive pregnancy: a retrospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology, 119(4):484–492.

Jasim, S., Al-Momen, H., Majeed, A., Hussein, M. 2018. Rate of Fetal Macrosomia with Maternal and Early Neonatal Complications in Internally Moved People Affected by Violence. 7:141–146.

Johnson, R. J., Kanbay, M., Kang, D. H., Sánchez-Lozada, L. G., Feig, D. 1979. Uric acid: a clinically useful marker to distinguish preeclampsia from gestational hypertension. Hypertension, 58(4):548–549.

Johnson, R. J., Merriman, T., Lanaspa, M. A. 2015. Causal or Noncausal Relationship of Uric Acid With Diabetes: Table 1. Diabetes. 64:2720–2722.

Khaliq, O. P., Konoshita, T., Moodley, J., Naicker, T. 2018. The Role of Uric Acid in Preeclampsia: Is Uric Acid a Causative Factor or a Sign of Preeclampsia? Current Hypertension Reports, 20(9).

King, C., Lanaspa, M. A., Jensen, T., Tolan, D. R., Sánchez-Lozada, L. G., Johnson, R. J. 2017. Uric Acid as a Cause of the Metabolic Syndrome. Contributions to Nephrology, 192:88–102.

Kratzer, J. T., Lanaspa, M. A., Murphy, M. N., Cicerchi, C., Graves, C. L., Tipton, P. A., Gaucher, E. A. 2014. Evolutionary history and metabolic insights

of ancient mammalian uricases. Proceedings of the National Academy of Sciences, 111(10):3763–3768.

Laughon, S. K., Catov, J., Powers, R. W., Roberts, J. M., Gandley, R. E. 2011. First Trimester Uric Acid and Adverse Pregnancy Outcomes. American Journal of Hypertension, 24(4):489–495.

Laughon, S. K., Catov, J., Roberts, J. M. 2009. Uric acid concentrations are associated with insulin resistance and birthweight in normotensive pregnant women. American Journal of Obstetrics and Gynecology, 201(6):1–582.

Liu, L., Yu, C., Yang, F., Yuan, Z., Wang, Q., Liu, S., Guan, Q. 2019. Maternal hyperuricemia superimposed on maternal hypertension aggravates the risk of small-for-gestational-age fetus. Life Sciences, 228:215–220.

Maged, A. M., Moety, G. A. F., Mostafa, W. A., Hamed, D. A. 2014. Comparative study between different biomarkers for early prediction of gestational diabetes mellitus. The Journal of Maternal-Fetal & Neonatal Medicine, 27(11):1108–1112.

Makinouchi, T., Sakata, K., Oishi, M., Tanaka, K., Nogawa, K., Watanabe, M., Suwazono, Y. 2016. Benchmark dose of alcohol consumption for development of hyperuricemia in Japanese male workers: An 8-year cohort study. Alcohol, 56:9–14.

Modan, M., Halkin, H., Karasik, A., Lusky, A. 1987. Elevated serum uric acid ? a facet of hyperinsulinaemia. Diabetologia, 30(9):713–718.

Moriyama, K. 2019. The Association Between the Serum Uric Acid to Creatinine Ratio and Metabolic Syndrome, Liver Function, and Alcohol Intake in Healthy Japanese Subjects. Metabolic Syndrome and Related Disorders, 17(7):380–387.

Nair, A., Savitha, C. 2017. Estimation of Serum Uric Acid as an Indicator of Severity of Preeclampsia and Perinatal Outcome. The Journal of Obstetrics and Gynecology of India, 67(2):109–118.

Rezk, M., Gaber, W., Shaheen, A., Nofal, A., Emara, M., Gamal, A., Badr, H. 2018. First versus second trimester mean platelet volume and uric acid for prediction of preeclampsia in women at moderate and low risk. Hypertension in Pregnancy, 37(3):111–117.

Ryu, A., Cho, N. J., Kim, Y. S., Lee, E. Y. 2019. Predictive value of serum uric acid levels for adverse perinatal outcomes in preeclampsia. Medicine, 98(18).

Shalal, M. M., Jasim, S. K., Shareef, R. M. 2017. The Polycystic Ovary Syndrome as A Cause of Increase in Inflammatory Markers and Metabolic Risks. Iraqi Postgraduate Medical Journal, 16(4).

Singh, U., Solanki, V., Mehrotra, S., Sharma, R. 2019. An Evaluation of Applicability of Salivary Uric Acid Measurement in Preeclampsia and Normal Pregnancy and Its Correlation with Serum Uric Acid. The Journal of Obstetrics and Gynecology of India, 69(1):62–68.

Tangren, J. S., Powe, C. E., Ecker, J., Bramham, K., Ankers, E., Karumanchi, S. A., Thadhani, R. 2018. Metabolic and Hypertensive Complications of Pregnancy in Women with Nephrolithiasis. Clinical Journal of the American Society of Nephrology, 13(4):612–619.

WHO 2006. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation.

Williams, K. P., Galerneau, F. 2002. The Role of Serum Uric Acid as a Prognostic Indicator of the Severity of Maternal and Fetal Complications in Hypertensive Pregnancies. Journal of Obstetrics and Gynaecology Canada, 24(8):30193–30194.

Zhou, G., Holzman, C., Luo, Z., Margerison, C. 2018. Maternal serum uric acid levels and blood pressure during pregnancy: A community-based cohort study. European Journal of Obstetrics & Gynecology and Reproductive Biology, 222:64–69.

Zhou, J., Zhao, X., Wang, Z., Hu, Y. 2012. Combination of lipids and uric acid in mid-second trimester can be used to predict adverse pregnancy outcomes. The Journal of Maternal-Fetal & Neonatal Medicine, 25(12):2633–2638.