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Maternal Serum Uric Acid as a Marker of Predicting Low Birth Weight at Term Pregnancy: A Study Based in CMH Lahore

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ABSTRACT

Objective: To determine the association of hyperuricemia with adverse pregnancy outcomes in terms of low birth weight at term pregnancy registered at CMH Lahore.
Study Design: Prospective cohort study.
Place and Duration of Study: Department of Obstetrics and Gynecology of CMH, Lahore Pakistan, from Aug 2018 to Feb 2019.
Methodology: A total of 60 pregnant women with a singleton pregnancy were included in the study. Patients with serum uric acid levels greater or equal to 360 umol/L were included in Group-A or the at-risk Group, and Patients with serum uric acid levels less than 360 umol/L were included in Group-B or the control Group. All women were followed till the delivery. Data regarding adverse pregnancy outcomes (low birth weight) was noted.
Results: Mean Serum uric acid levels of 380.33±12.92 umol/L in the Exposed Group and mean Serum uric acid levels of 265.66±29.44 umol/L in the Control Group were noted. Low birth weight was seen 12 (40%) in Exposed Group as compared to 7(23.3%) in Unexposed Group (p=0.165) (RR=1.71).
Conclusion: Low birth weight at term was not associated with hyperuricemic pregnancy more than normouricemic pregnancy in our study, probably due to the small sample size.

Keywords: Hyperuricemia, Low birth weight, Pregnancy.

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INTRODUCTION

Low birth weight is defined as weight at birth less than 2500 grams at term. Low birth weight has long been an important public health care indicator. It is a good measure of adverse outcomes regarding maternal and perinatal health and provides a summary of multiple health care problems worldwide.[1] Public healthcare problems like poor maternal health, malnutrition, adverse work and social settings are highlighted by the population's index of low birth weight. While there have been extensive studies on the epidemiology of low birth weight, it remains less researched in developed countries resulting in no significantly reliable data on the subject.[2] The scarcity of research in our local population on this subject is a compelling argument to gather more data regarding birth weight. The existing research and data have been mainly focused on the relation between hyperuricemia and low birth weight in certain medical conditions, such as chronic hypertension, renal disease, and multiple gestations, all of which have been shown to affect uric acid levels and pregnancy outcomes.[3] However, do serum uric acid levels affect pregnancy outcomes independently, without any preexisting medical or gestational conditions? This question remains to be answered. Low birth weight is one of the leading causes of neonatal morbidity and mortality in developing countries.[4] This study aimed to early detect pregnant women at high risk of having adverse pregnancy outcomes in low birth weight neonates. Early detection will help with antenatal monitoring, planning and management and thus reduce adverse pregnancy outcomes.

As an end product of purine metabolites, serum Uric acid (UA) levels are under the influence of many factors.[5] Excess uric acid levels result in many pathological manifestations by initiating a complex proinflammatory cascade and compliment activation.[6]

The normal range of serum uric acid levels in females is 140-360 µmol/L. Exogenous factors such as high intake in the diet, decreased water intake, Alcohol, and endogenous causes, including liver, and renal diseases, all contribute to hyperuricemia.[7]

A strong association between hyperuricemia and adverse pregnancy outcomes has been established in many studies. It is an important independent measure of the risk of preterm birth, low birth weight (LBW)

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and low one and 5-minute APGAR scores.[8] Through activation of pro-inflammatory mediators, hyperuricemia can impede amino acid transfer to the fetus, thus affecting fetal growth.[9] In neonates, it is associated with neonatal morbidity and mortality. In addition, maternal hyperuricemia can lead to Preterm delivery and Intra-ventricular Hemorrhage in neonates.[10] Prevous studies' findings paved the way for researchers to recommend screening for hyperuricemia during pregnancy, using it as an indicator for potential risks and thus using it to predict, identify and attempt to prevent and lower adverse pregnancy outcomes.

METHODOLOGY

This prospective cohort study was carried out at the Department of Obstetrics and Gynecology, Combined Military Hospital Lahore Pakistan, from August 2018 to February 2019. A sample size of 60 (30 in each Group) was calculated at a 5% level of significance, 80% power of the test and taking expected frequency of low birth weight in the hyperuricemic Group as 56% and without hyperuricemia Group as 21%.[4] A non-probability consecutive sampling technique was used.

Inclusion Criteria: Pregnant women aged 18-35 years, gestational age equal to or less than 20 weeks by last menstrual period, Parity 0-4 were included in the study. Patients with serum uric acid level greater or equal to 360 umol/L were included in Group-A or the Exposed Group, Patients with serum uric acid level less than 360 umol/L were included in Group-B or Non Exposed Group.

Exclusion Criteria: Patients with the history of renal disease on the medical record, smokers (>5 cigarettes per day for last year), multiple gestations, history of chronic hypertension on the medical record, women using drugs affecting uric acid levels, history of diabetes on the medical record were excluded in the study.

A total of 60 women fulfilling the inclusion criteria from the Outdoor Patient Department, CMH Lahore, were included in the study after permission from the Ethical Committee of CMH Lahore. Basic demographics were noted, and detailed informed consent was taken, ensuring the confidentiality of the patients. No risk was involved to the patient taking part in the study. The women were divided into two equal Groups. 30 sample size for Group-A or hyperuricemic Group while 30 for Group-B or normaluricemic Group-. Detailed history and general physical and clinical examination were made. Details of examination and investigation like serum uric acid levels were noted on structured performance. All women were followed till delivery. Data regarding adverse pregnancy outcomes (low birth weight) were noted by the researcher herself on specially designed proforma.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Mean ± SD were calculated for quantitative variables like age, gestational age, and serum uric acid levels. Frequency and percentage were calculated for qualitative variables like low birth weight. Parity was calculated as frequency. Relative risk was also calculated to measure the significance of the association. A relative risk of > 1 was considered significant. Association was seen using the chi-square test, and relative risk for both Groups was calculated.

RESULTS

The Group of 60 pregnant women placed in two Groups, exposed and unexposed according to their serum uric acid, were further stratified according to their age, gestational age and parity and their outcome in terms of low birth weight were compared. Patients' age ranged from 18 to 35 years, with a mean age of 28.400±3.01 years, mean gestational age of 13.86±3.40 weeks, and mean Serum uric acid levels of 380.33± 12.92 umol/L in the exposed Group and mean age of 29.000±2.74 years, mean gestational age 15.600±2.06 weeks and mean serum uric acid levels 265.666±29.44 umol/L in the unexposed Group.

Parity 0-2 was dominant in both Groups, 25 (83%) & 23 (73%) respectively. Low birth weight was seen in 12 (40%) in the exposed Group- as compared to 7 (23.3%) in the unexposed Group (p-0.165) (R.R 1.71), as shown in Table-I.

Table-I: Frequency of Low Birth Weight in Both Groups (n=60)

Low Birth Weight	Exposed Group n=30 n (%)	Unexposed Group n=30 n (%)	p-value	Relative Risk
Yes	12 (40.0)	7 (23.3)	0.165	1.71
No	18 (60.0)	23 (76.7%)		

Table-II showed low birth weight in exposed and unexposed Groups with maternal age, gestational age, and parity.

DISCUSSION

Our study studied the correlation between hyperuricemia in pregnant women and Low birth weight. Low birth weight was seen in 12 (40%) patients in the exposed Group as compared to 7 (23.3%) in the unexposed Group (p=0.165) (R.R=1.71). The small sample

size in our study can be accredited to the unsubstantiated association between maternal hyperemia and low birth weight as no significant association was seen.

Table-II: Association of Low Birth Weight with Hyperuricemia in Relation to Maternal Age, Gestational Age And Parity, In Both Groups

Parameters	Low Birth Weight		*p*-value	Relative Risk
AGE 18-27 Years	Yes n (%)	No n (%)		
Exposed (n=8)	4 (50.0)	4 (50.0)	0.782	0.87
Unexposed (n=7)	4 (57.1)	3 (42.9)		
AGE 28-35 years				
Exposed (n=21)	8 (36.4)	14 (63.6)	0.068	2.78
Unexposed (n=23)	3 (13.0)	20 (87.0)		
Gestational Age 6-12 weeks				
Exposed (n=10)	3 (30.0)	7 (70.0)	0.48	0.6
Unexposed (n=7)	2 (50.0)	2 (50.0)		
Gestational Age 13-20 weeks				
Exposed (n=20)	9 (45.0)	11 (55.0)	0.059	2.34
Unexposed (26)	5 (19.0)	21 (80.0)		
Parity 0-2				
Exposed (n=25)	10 (40.0)	15 (60.0)	0.205	1.76
Unexposed (n=22)	5 (22.7)	17 (77.3)		
Parity 3-4				
Exposed (n=5)	2 (40.0)	3 (60.0)	0.568	1.6
Unexposed (n=8)	2 (25.0)	6 (75.0)		

In comparison, in a case-control study at Okayama University Hospital, in 2009, Akahori *et al.* concluded that maternal hyperuricemia was inversely related to fetal growth and neonatal birth weight (r=0.59; *p*=0.006).[4] They compared a Group of 40 pregnant women with small for gestation age (SGA) babies to a Group of 80 pregnant women having appropriate for gestation age (AGA) babies and found a significant correlation between maternal hyperuricemia and LBW. In a prospective cohort study conducted at Tehran University of medical sciences from 2011 to 2012, Amini *et al.* emphasized the independent association of maternal hyperuricemia with preterm delivery (*p*< 0.001), SGA and LBW (*p*=0.02), Low 1- and 5-minute APGAR scores (*p*=0.004), prolonged NICU stay (*p*= 0.002), neonatal hypoglycemia (*p*=0.009) and neonatal intraventricular haemorrhage (IVH) (*p* = 0.007).[8] In that same study, 103 (25.4%) women were detected to have hyperuricemia and, more commonly, at younger maternal age (*p*= 0.005) and primigravida (*p* = 0.04).[8] In our study, however, the increased association was found in increasing age of the patients, 8% in exposed women aged 28 to 35 years as compared to 3% in unexposed in the same age bracket (*p*=0.06) (R.R=2.78). Primigravida was not included in a separate Group- but in a low parity Group, and an increased association of low birth weight with primigravida in exposed (40%) was seen, as compared to unexposed (22.7%) (*p*=0.205) (R.R=1.76). In a study by Tejal *et al*. the frequency of Preterm births was 20% in hyperuricemic pregnancy compared to 4% in normal pregnancy.[9] Preterm birth was in exclusion criteria in our study. The effects of maternal hyperuricemia on fetal weight have also been reported by Laughon *et al.* in 2009, in a study that established a correlation between low birth weight and hyperuricemia due to attenuating effects of raised uric acid levels on insulin resistance.[10] A similar study, carried out in Taleghani Hospital (Arak, Iran) from 2010 to 2012, as reported by Nasri *et al*. however, showed that hyperuricemia was also associated with low birth pregnant women with no evident insulin resistance (*p*=0.05, r=-0.2).[11] Rewatkir *et al.* at Indira Gandhi Government medical college and hospital, India, conducted a study designed to establish an association between maternal hyperuricemia and adverse pregnancy outcomes.[12] Out of 63 pregnant women with hyperuricemia, 29 women delivered LBW babies. The study safely concluded that serum uric acid is an early marker for preterm delivery, LBW and fetal compromise.

Extensive research has been done in the past, internationally as well as locally, identifying maternal hyperuricemia as a marker of adverse maternal and neonatal outcomes in high-risk pregnancies such as hypertensive disorders of pregnancy, diabetes, and pregnancy with chronic kidney disease. In a study by Lin *et al.* from 2015 to 2017, 180 pregnant women with hypertensive disease of pregnancy were put into two sub Group-s based on their uric acid levels.[13] One Group- had raised maternal serum uric acid (n=137), and the other had normal levels (n=43). The pregnancy outcomes were compared with another Group of 180 healthy pregnant women. Their results showed that maternal hyperuricemia (uric acid>357umol/L) is an indicator of adverse pregnancy outcomes in women with hypertensive disease of pregnancy (OR=1.258, *p*< 0.05). In their study, Singh *et al.* showed that the frequency of low birth weight was 27.9% in hyperuricemic pregnancy complicated by hypertension compared to 21% in normal healthy pregnancy.[14] Clinical studies have also linked uric acid levels to activation of the renin-angiotensin system,[15] increased vascular stiffness,[16] and increased sympathetic activity.[17] A strong association between first-trimester maternal hyperuricemia and gestational diabetes mellitus (GDM) was

found in a study conducted at Pak Emirates Military Hospital, Pakistan, from 2015 to 2016 by Ismail *et al.* [18] The study concluded that the prevalence of GDM was 50-51 % in women with hyperuricemia detected in the first trimester. A similar study by Rehman *et al*. conducted at CMH, LHR, concluded that the diagnostic accuracy of first-trimester hyperuricemia to predict GDM was 94.5 %.[19] Although these studies conclude significantly and substantially that maternal hyperuricemia has a positive role in predicting and screening adverse maternal and neonatal outcomes in high-risk pregnancies, the role of maternal hyperuricemia as an independent factor in adverse pregnancy outcomes requires much more research. In our study, we aimed to signify the role of maternal hyperuricemia as an independent risk factor for LBW.

Excluding pre-existing certain medical conditions from our cohort was done to emphasize maternal hyperuricemia independent of any other risk factors. However, much more domestic and worldwide research is required on larger samples to substantiate the role of hyperuricemia as an independent screening factor for predicting LWB. After all, LBW remains the most magnanimous of health care problems in the developing world's pregnant population and deserves all efforts to predict and thereby reduce its incidence.

CONCLUSION

No significant association is seen between maternal hyperuricemia and low birth weight at term pregnancy. Therefore, maternal serum uric acid may not be an early marker for low birth weight in normal pregnancy until larger studies are conducted.

Conflict of Interest: None.

Author's Contribution

SG: Study topic, stay design and conduct, ZS: Literature review and abstract, QN: Data analysis, SS: Data collection, SS: Discussion, NT: Introduction.

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