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RELATIONSHIP BETWEEN HYPERURICEMIA AND PERINATAL OUTCOMES AMONG PREGNANT HYPERTENSIVE WOMEN

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ABSTRACT

This study aimed to determine the relationship between hyperuricemia and perinatal outcome in pregnancy induced hypertension. This prospective and observational study was carried out in Al-Falluja Teaching Hospital for Gynecology and Pediatrics – Falluja-Anbar /Iraq. The study included (75) primigravida female patients in the third trimester (after 32 weeks gestation) with pregnancy induced hypertension. Serum uric acid assay was done then the patients were classified into three groups according to uric acid levels; Group I (low hyperuricemia) uric acid below 25th percentile (<3.7 mg/dl), group II (middle hyperuricemia) uric acid from 25th to 75th percentile (3.8 to 5.7 mg/dl) and group III (high hyperuricemia) uric acid above 75th percentile (>5.8 mg/dl). The maternal outcome was followed up as (eclampsia, HELLP, acute renal failure and accidental hemorrhage) and fetal out- comes (stillbirth, prematurity, IUGR and IUFD). The results showed statistically significant increase of serum uric acid, urea and creatinine in high group compared to middle and low ones. Bad fetal outcome and pregnancy complications were directly proportional to the serum uric acid levels. It can be concluded for our study that hyperuricemia may be used in the prognosis of adverse perinatal outcomes in pregnancy induced hypertension, and that serum uric acid levels is a useful and inexpensive marker for predicting adverse perinatal outcomes.

KEYWORDS: Serum uric acid; Hyperuricemia; Preeclampsia; Pregnancy induced hypertension.

INTRODUCTION

Hypertensive disorder of pregnancy is responsible for significant amount of maternal and perinatal morbidity and mortality. Pregnancy may induce hypertension in women who are normotensive before pregnancy and may aggravate hypertension in those that were hypertensive.[1,2] Despite advances in care, preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality world- wide.[3] Preeclampsia affects multiple organ systems and can lead to sever renal, hepatic, neurological and cardiopulmonary complications. Often the fetus is affected, and adverse prenatal outcomes include preterm birth, intrauterine growth restriction, and death. Ultimately, delivery is the only definitive treatment for severe preeclampsia; however, many cases can be managed expectantly with increased maternal and fetal monitoring, maternal blood pressure control, and maternal seizure prophylaxis.[3]

The challenge in caring for women with preeclampsia is to identify those who are at increased risk for complications so that appropriate and timed delivery can be offered. The preeclampsia integrated estimate of risk research program was conceived to address this critical need in preeclampsia management. Using a combination of maternal demographics, signs, symptoms and laboratory findings, the full PIERS model can successfully identify women at risk for preeclampsia complications so that they can access appropriate care worldwide.[4,5] Hypertension in pregnancy is also responsible for 18% of fetal and infant mortality and 46% of infants born small for gestational age.[6-8] Early screening for preeclampsia may allow antenatal surveillance and appropriate timing of fetal delivery in order to avoid serious sequelae.[9] Unfortunately, various hemodynamic and biochemical measures have been found to have limited accuracy as screening measures for this condition. Elevated uric acid level in maternal blood, presumably due to decreased renal urate excretion, are frequently found in women with preeclampsia.[9]

Various studies of serum uric acid level in normal and hypertensive pregnancy and its relation with the early diagnosis of preeclampsia, severity of preeclampsia and

associated perinatal outcome have been done in many parts of the world.[10-12]

It has been mostly accepted that hyperuricemia in women with preeclampsia is primarily a result of a reduction in glomerular filtration rate, although others have suggested a possible role for elevated uric acid levels in the pathogenesis of preeclampsia, via endothelial dysfunction.[13-15]

PATIENTS AND METHODS

This prospective and observational study was carried out in Al-Falluja Teaching Hospital for Gynecology and Pediatrics – Falluja-Anbar /Iraq. The study included 75 pregnant women with pregnancy induced hypertension.

Primigravida patient in the third trimester were (this confirmed by ultrasound) presented with pregnancy induced hypertension (PIH) (blood pressure ≥140/90 mmHg) which was measured by mercury sphygmomanometer and three readings were taken at 10 minutes interval average systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

Systolic blood pressure (SBP) of 160 mm Hg or higher or diastolic blood pressure (DBP) of 110 mm Hg or higher, on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy has previously been initiated) were recorded. Impaired hepatic function as indicated by abnormally elevated blood level of liver enzymes (to double the normal concentration), severe persistent upper quadrant or epigastric pain that does not respond to pharmacotherapy and is not accounted for by alternative diagnoses, or both, progressive renal insufficiency (serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease), new onset cerebral or visual disturbances, pulmonary edema and thrombocytopenia (platelet count <100,000/cm3, all were excluded.

All cases were subjected to; a detailed history to detect medical diseases such as chronic hypertension, diabetes, pulmonary diseases, renal disorders or other diseases affecting fetal growth. Also, family history of congenital malformation or chromosomal abnormalities was taken in consideration, obstetric history was taken to detect previous growth restricted baby, malformed or stillbirth. Physical examination was done to detect hypertension, heart diseases, chest diseases or other medical disorders. Transabdominal ultrasound for assessment of fetal wellbeing was done. Laboratory investigations included complete blood picture, fasting and postprandial blood sugar, liver function tests, renal function test and serum uric acid assay.

All patients enrolled in the study were classified into three groups according to uric acid level; Group I (25 cases) (low hyperuricemia) uric acid below 25th percentile (<3.7 mg/dL), group II (20 cases) (middle hyperuricemia) uric acid from 25th to 75th percentile (3.8 to 5.7 mg/dL) and group III (30) cases (high hyperuricemia) uric acid above 75th percentile (>5.8 mg/dL). Maternal and fetal outcomes were followed up.

RESULTS

Table (1): The demographic data of three studied groups.

		Range	Mean±S. D	F. test	P Value		
Uric acid	Low	2.4 – 3.5	3.21±0.14	578.08	0.001*	P1	0.005*
	Middle	3.7 – 4.3	4.14±0.11			P2	0.005*
	High	6.1 - 9.1	7.45±0.75			P3	0.005*
Urea	Low	21 – 33	26.13±2.51	253.90	0.001*	P1	0.095
	Middle	25 – 36	29.14±2.42			P2	0.005*
	High	26 – 69	46.94±4.98			P3	0.005*
Creatinine	Low	0.5 – 0.8	0.61±0.11	75.612	0.001*	P1	0.755
	Middle	0.5 – 0.9	0.65±0.10			P2	0.005*
	High	0.5 – 1.3	0.99±0.15			P3	0.005*
The serum uric acid, urea and creatinine are significantly elevated in high group compared to middle and low groups. P1: Low& Middle P2 Low& High P2 Middle & High							

Table (2): Fetal outcomes in the three studied groups.

Fetal outcome		Low (N=25)	Middle (N=20)	High (N=30)	Total
Good	N	22	18	18	58
	%	88.0%	90.0%	60.0%	80%
Bad	N	3	2	12	17
	%	12.0%	10.0%	40.0%	20.0%
Total	N	25	20	30	75
	%	100.0%	100.0%	100.0%	100.0%

Chi-square	X^2	8.595
	p Value	0.013*
This table demonstrates good outcome fetuses (full-term, no need for NICU and no IUGR), bad outcome fetuses (IUGR, stillbirth, NICU and preterm baby) that more in high group.		

Table (3): Maternal outcome of the studied groups.

Maternal outcome		low	Middle	High	Total
No complications	N	25	18	17	60
	%	100.0%	90.0%	56.7%	80.0%
Eclampsia	N	0	2	5	7
	%	.0%	10.0%	16.7%	9.3%
Accidental hemorrhage	N	0	0	2	2
	%	0%	0%	6.7%	2.7%
HELLP	N	0	0	2	2
	%	.0%	0%	6.7%	2.7%
ICRU	N	0	0	2	2
	%	0%	0%	6.7%	2.7%
ARF	N	0	0	2	2
	%	0%	0%	6.7%	2.7%
Total	N	25	20	30	75
	%	100.0%	100.0%	100.0%	100.0%
Chi-square	X2	19.61			
	P Value	0.033*			
This table shows no complication in low level uric acid mothers, more complications were observed in high uric acid serum level associated with pregnancy induced hypertension					

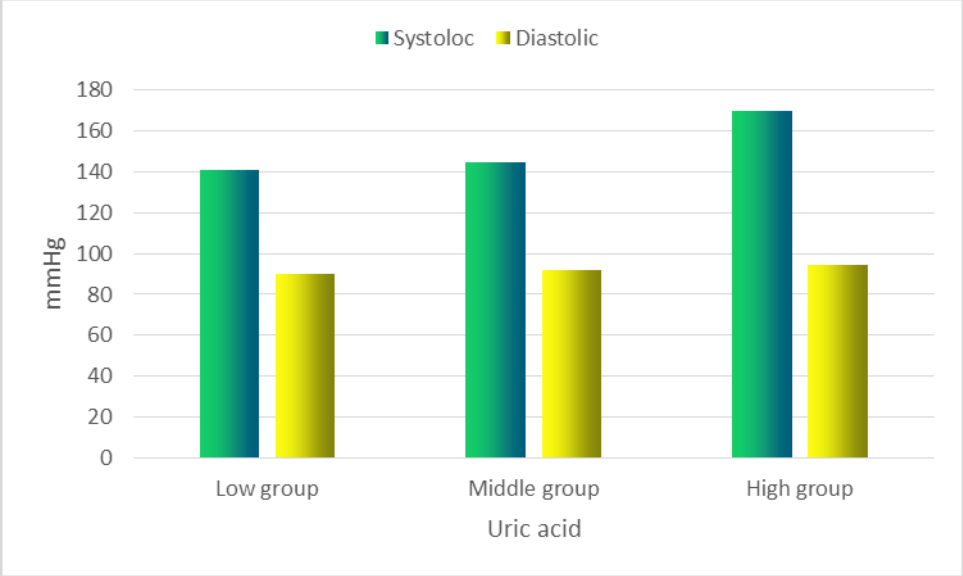

Figure (1): Blood pressure distribution among uric acid groups.

DISCUSSION

Gestational hypertension is a medical disorder worldwide that complicates approximately 12-22% of the pregnancies.[16] Interpretation of uric acid level requires the exact knowledge of the duration of gestation, as its levels in normal pregnancy increase with the increasing gestation period, i.e. 2-4.2 mg/dL, 2.4-4.9 mg/ dL and 3.1-6.3 mg/dL in 1st, 2nd and 3rd trimester of pregnancy re- spectively.[17] Women with gestational hypertension and hyperuricemia have evidence of endothelial dysfunction and deliver growth- retarded babies.[18]

In our study 75 pregnant women with pregnancy induced hypertension were subjected to evaluate serum uric acid at the moment of hypertension diagnosis. In this study, the mean age for the low group was (24.54±1.95), (25.10±3.12) for the middle group and (26.54±3.95) for the high group and there was no significant difference between the three groups (p=0.062) .The mean gestational age for the low group was (35.25±1.98), (35.54±1.79) for the middle group and (35.16±2.08) for

the high group. There was no significant difference between the mean of the three groups (p =0.795).

Aneela Khaleeq et al.[19] agreed with us as there was no significant difference between studied groups. In group A uric acid ranged from 2.7 to 5.3 mg/dL while in group B, it ranged from 5.9 to 9.9 mg/dL as regard to age and gestational period.

Kaur P et al.[20] showed that systolic as well as diastolic blood pressure levels in preeclamptic women (150.8±8.6 mmHg, 101.3±8.01 mmHg) were much higher than that of normal pregnant women (114.3±8.6 mmHg, 74.4±6.9 mmHg). This difference was found to be very highly significant (p=0.0001). It was also observed by,[21] that uric acid level was within moderate increase range in 58% patients in the preeclamptic group and 84% patients of the control group, whereas it is above the upper limit of normal range (i.e. >6 mg%) in 42% patients of study group and 2% patients in control group, the mean value of serum uric acid level in study group was 5.8+1.8 mg% which is quite higher than that of the control group i.e.(4.1±1.05 mg% and this difference was statistically significant (p=0.0001).

Apeksha et al,[22] found that Serum uric acid was significantly higher in the PIH group (5.46±1.51) compared to the control group (4.03±0.69). On the other hand, serum creatinine and urea were approximately similar in between the groups as serum creatinine in PIH group was (0.50±36) and in the control group was (0.49±0.14), urea in PIH group (15.77±6.35) control group (15.28±4.70).

Escudero et al,[23] agreed with us, as women with high uric acid levels showed a longer-hospitalization period (1.2 days more), less platelet count (103/ml) and high creatinine plasma levels (0.2 mg/dL) compared to women with low-levels.

Bad fetal outcome is directly proportional to the serum uric acid level. In high group, it is (40.0%) compared to (12.0%) of the low group and (10.0%) of the middle group with p value (0.013). These results were comparable to those of AU Hosna et al,[21] who classified the patients according to uric acid into 3 groups (group A>5mg/dL, group B5-6.9 and group C>7mg/dL) to see the effect on fetal outcome. In (group A) (63.1%) fetus were found with good out come and (23.7%) with bad outcome, (group B) (27.7%) with good out- come and (32.2%) with bad outcome (group C) (9.2%) with good outcome and (44.1%) with bad outcome.

These results are also comparable to those of Aneela Khaleeq et al who,[19] who showed that serum uric acid level measurement is a useful and inexpensive marker for predicting preeclampsia and fetal growth retardation in women suffering from gestational hypertension. The mean uric acid level in group A was 3.64±0.73 mg/dL and in group B was 7.98±0.85 mg/dL. In group A, 9.3% newborns were found small-for-gestational-age (SGA), whereas in Group B, 23.3% newborns were found to be SGA. The relative risk was calculated for development of SGA in hyperuricemia and was found significant.

Moreover, in pregnancy outcomes overview of Amini et al,[24] 59 women gave birth to a small for gestational age (SGA) neonate (birth weight <10th percentile for gestational age (11.3%). Seventy-nine neonates required NICU admission (19.5%). Forty neonates had low 1-minute Apgar scores, and 40 neonates had low 5-minute Apgar scores (Apgar score <7) (9.9%). Twenty-seven required resuscitation in the delivery room (6.6%). Seven neonates developed IVH (1.7%) and 16 neonates suffered from respiratory distress syndrome (RDS) (3.9%). Maternal hyperuricemia in normotensive singlet on pregnant women constitutes a risk factor for adverse pregnancy outcomes and the development of neonatal hypoglycemia and intraventricular hemorrhage.

In addition, Kondareddy T et al,[25] revealed 165 fetuses with good outcome (65.50%) in group A (uric acid<6mg/dL) and (34.50%) in group B (uric acid≥6mg/dL). While bad outcome IUGR (36) (19.40% in group A and 80.60% in group B). Still birth (7) all in group B. NICU (41) (29.30% in group A and 70.70% in group B), preterm (28.12% in group A and 71.90% in group B).

In a study conducted by J. Dhaka et al, [26] the relationship of high blood uric acid in preeclamptic women with poor fetal outcome (low birth weight (LBW) fetus and stillbirth) was observed. In hyperuricemic subjects serum uric acid concentration was 7.09±1.09 mg/dL and in normouricemic group it was 4.62±0.76 mg/dL. There were significant differences of the uric acid levels between the two groups. In hyperuricemic group, (20%) fetuses were of normal birth weight and (72%) fetuses were of low birth weight.

Adverse maternal outcome in our study related more to hypertension and hyperurecimia than women with low uric acid level. None of low-level uric acid mothers were complicated, while complicated cases in middle group were (10.0%) and (43.3%) in high group. Eclamptic cases were (10.0%) in middle group and (16.7%) in high group. Accidental hemorrhage presented in only (6.7%) of high group, HELLP syndrome was in (6.7%) of high group, acute renal failure in (6.7%) of high group and intensive care unit admission (ICRU) in high group was (6.7%) More complications were observed in high uric acid serum level associated with pregnancy induced hypertension and the results were significant (p=0.033).

These results are comparable to those of Kondareddy T et al,[25] who showed accidental hemorrhage case (0.9%) in group A uric acid A<6 mg/dL and 7 (87.5%) in group B uric acid ≥6mg/ dL). Acute renal failure only one case (16.7%) in group A and 5 (83.3%) in group B. Eclampsia (34) (7 (20.6) in group uric acid A and 27 (79.4%) in

group B. HELLP (only one case (9.1%) in group A and 10 (90.9%) in group B). Mortality (1) only one case in group B.

Hawkins et al,[27] showed that maternal hyperuricaemia, measured near delivery is associated with adverse maternal and fetal outcomes. Hyperuricaemia is associated with an increased prevalence of small for gestational age (SGA) infants and prematurity. Observations suggest that gestational hypertension in the presence of hyperuricaemia is a disease with increased fetal risk.

REFERENCES

1. Muti M, Tshimanga M, Gombe N, Chonzi P. Prevalence of pregnancy induced hypertension and pregnancy outcomes among women seeking maternity services in Harare, Zimbabwe. BMC Cardiovascular Disorders, 2015; 15: 111. doi: 10.1186/s12872-015-0110-5.
2. Lin S, Leonard D, Co MA, et al. Pre-eclampsia has an adverse impact on maternal and fetal health. Transl Res., 2015; 165(4): 449- 63. doi: 10.1016/j.trsl.2014.10.006.
3. Nardozza LMM, Caetano AC, Zamarian ACP, et al. Fetal growth restriction: Current knowledge. Arch Gynecol Obstet, 2017; 295: 1061-1077. doi: 10.1007/s00404-017-4341-9.
4. Von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in preeclampsia: Developmentand validation of the full PIERS model. Lancet, 2011; 377: 219-227. doi: 10.1016/ S0140-6736(10)61351-7
5. Magee LA, Pels A, Helewa M, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens, 2014; 4 (2): 105-145. doi: 10.1016/j.preghy.2014.01.003
6. Goldenberg RL, Jones B, Griffin JB, et al. Reducing maternal mortality from preeclampsia and eclampsia in low-resource coun- tries - what should work? Acta Obstet Gynecol Scand, 2015; 94(2): 148-155. doi: 10.1111/aogs.12533.
7. Claven T, Djurovic S, Henriksen T. Dyslipidemia in early 2nd tri- mester is mainly a feature of women with early onset preeclampsia BJOG, 2001; 108(10); 1081-1087.
8. Damien S, Patric G, Francies P, et al. Aspirin (100mg) used for prevention of preeclampsiain nulliparous women: The Essai Re- gional Aspirin Mere - Enfant study (Part-1). BJOG, 2003; 110: 475- 484.
9. Shaker el Sayed Azzaz AM. Antenatal care booking during preg- nancy and its effect on maternal and fetal outcomes. (Doctoral thesis). Universidad de Sevilla, Sevilla, 2017.
10. von Dadelszen P, Magee LA. Preventing deaths due to the hy- pertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynae- col, 2016; 36: 83-102. doi: 10.1016/j.bpobgyn.2016.05.005.
11. Livingston JR, Payne B, Brown M, et al. Uric Acid as a predic- tor of adverse maternal and perinatal outcomes in women hospi- talized with preeclampsia. J Obstet Gynaecol Can, 2014; 36(10): 870- 877. doi: 10.1016/S1701-2163(15)304357.
12. Zhou G, Holzman C, Luo Z, Margerison C. Maternal serum uric acid levels and blood pressure during pregnancy: A community-based cohort study. Eur J Obstet Gynecol Reprod Biol., 2018; 222: 64-69. doi: 10.1016/j.ejogrb.2018.01.008.
13. Kang DH, Finch J, Nakagawa T, et al. Uric acid, endothelial dysfunction and preeclampsia: Searching for a pathogenetic link. J Hypertens, 2004; 22(2): 229-235.
14. Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in preeclampsia. Placenta, 2008; 29(Suppl A): S67-S72. doi: 10.1016/j. placenta.2007.11.001.
15. Martin AC, Brown MA. Could uric acid have a pathogenic role in pre-clampsia? Nat Rev Nephrol, 2010; 6: 744-748. doi: 10.1038/ nrneph.2010.125
16. Lisonkova S, Sabr Y, Mayer C, et al. Maternal morbidity associ- ated with early-onset and late-onset preeclampsia. Obstet Gynecol, 2014; 124: 771-781. doi: 10.1097/AOG.0000000000000472.
17. Wolak T, Sergienko R, Wiznitzer A, Paran E. High uric acid level during the first 20 weeks of pregnancy is associated with higher risk for gestational diabetes mellitus and mild preeclampsia. Hypertens Pregnancy, 2012; 31: 307-315. doi: 10.3109/10641955.2010.507848.
18. Phad N, Dahlstrom JE, Ellwood D, Kent AL. The effect of pregnancy-induced hypertensive disorders on placental growth along short and long axes and neonatal outcomes. Aust N Z J Obstet Gynaecol, 2015; 55: 239-244. doi: 10.1111/ajo.12308.
19. Khaleeq A, Waheed K, Ejaz S, Kamal A. Hyperuricemia as a predictor of poor fetal outcome in pre-eclamptic women. Journal of Rawalpindi Medical College (JRMC), 2015; 171-173.
20. Patel K, Kaur P, Deepak A, et al. Association of serum uric acid and C-reactive protein levels in prediction of preeclampsia. Int J Reprod Contracept Obstet Gynecol, 2016; 5(2): 495-502. doi: 10.18203/2320-1770.ijrcog20160398.
21. Ul Hosna A, Bhuiyan AKMM, E-Ferdous N, et al. Effects of hyperuricemia on perinatal outcome in hypertensive disorder of pregnancy. University Heart Journal, 2008; 4(2): 36-40. doi: 10.3329/ uhj.v4i2.2074.
22. Niraula A, Lamsal M, Majhi S, Khan SA, Basnet P. Significance of serum uric acid in pregnancy induced hypertension. J Natl Med Assoc, 2017; 109(3): 198-202. doi: 10.1016/j.jnma.2017.01.009.
23. Escudero C, Bertoglia P, Acurio J, Escudero A. Hyperuricemia in the prognosis of adverse perinatal outcomes: An International. Journal of Women's Cardiovascular Health, 2012; 2: 240-339.
24. Amini E, Sheikh M, Hantoushzadeh S. Maternal hyperuricemia in normotensive singleton pregnancy,

a prenatal finding with con- tinuous perinatal and postnatal effects. BMC Pregnancy Childbirth, 2014; 14: 104. doi: 10.1186/1471-2393-14-104.

25. Kondareddy T, Prathap T. Uric acid as an important biomarker in hypertensive disorders in pregnancy. Int J Reprod Contracept Obstet Gynecol, 2016; 5(12): 4382-4384. doi: 10.18203/2320-1770. ijrcog20164348.
26. Hussain SS, Choudhury MBK, Akhter J, et al. Fetal outcome of pre-eclamptic mothers with hyperuricemia. J Dhaka National Med. Coll. Hos, 2011; 17 (01): 41-43. doi: 10.3329/jdnmch. v17i1.12192.
27. Hawkins T, Roberts J, Mangos G, et al. Plasma uric acid remains a marker of poor outcome in hypertensive pregnancy: A retro- spective cohort study. BJOG, 2012; 484-492. doi: 10.1111/j.1471-0528.2011.03232.x