

**Original Research****Pregnancy-Induced Hypertension: Hyperuricemia as a Predictor of Perinatal Outcomes**

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**ABSTRACT****Aim/Objective**

The aim of this study to determine the relationship between hyperuricemia and perinatal outcome in pregnancy induced hypertension.

**Material & Methods**

This prospective and observational study was carried out in the Department of Obstetrics & Gynecology of Tanta University. The study included (100) 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 level; Group I (low hyperuricemia) uric acid below 25<sup>th</sup> percentile (<3.7 mg/dl), group II (middle hyperuricemia) uric acid from 25<sup>th</sup> to 75<sup>th</sup> percentile (3.8 to 5.7 mg/dl) and group III (high hyperuricemia) uric acid above 75<sup>th</sup> percentile (>5.8 mg/dl).

Follow up of maternal outcome as (eclampsia, HELLP, acute renal failure and accidental hemorrhage) and fetal outcomes (stillbirth, prematurity, IUGR and IUFD).

Other obstetric complication that can affect pregnancy, other medical disease and severe pre-eclampsia that need urgent termination were excluded.

**Result**

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 proportionate to the serum uric acid level.

**Conclusion**

These data reinforce the general agreement about the utility of hyperuricemia in the prognosis of adverse perinatal outcomes in pregnancy induced hypertension. Serum uric acid level measurements are a useful and inexpensive marker for predicting adverse perinatal outcomes.

**Keywords**

Serum uric acid; Hyperuricemia; Pre-eclampsia; 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.<sup>1,2</sup>

Despite advances in care, preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwide.<sup>3</sup>

Preeclampsia affects multiple organ systems and can lead to severe 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.<sup>3</sup>

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.<sup>4,5</sup>

Confirm that hypertensive disorder of pregnancy is still the 2<sup>nd</sup> most common cause of maternal mortality, accounting for 15.5% direct death. Hypertension in pregnancy is also responsible for 18% of fetal and infant mortality and 46% of infants born small for gestational age.<sup>6-8</sup>

Early screening for preeclampsia may allow antenatal surveillance and appropriate timing of fetal delivery in order to avoid serious sequelae.<sup>9</sup> 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.<sup>9</sup>

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.<sup>10-12</sup>

A frequently reported laboratory finding in women with preeclampsia is elevated serum uric acid. Most accept 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.<sup>13-15</sup>

This study was conducted to determine the relationship between hyperuricemia and perinatal outcomes in pregnancy induced hypertension.

## PATIENTS AND METHODS

This prospective and observational study was carried out in the Department of Obstetrics & Gynecology of Tanta University, Tanta, Egypt. The study included 100 pregnant women with pregnancy induced hypertension.

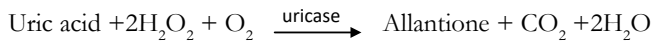
Primigravida patient in the third trimester were (this confirmed by ultrasound), presented with pregnancy induced hypertension (PIH) (blood pressure  $\geq 140/90$  mmHg), it was measured by mercury sphygmomanometer in reclining position in right brachial artery, three readings were taken at 10 minutes interval average systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg .

Exclusion criteria was other obstetric complication can affect pregnancy (e.g. premature rupture of membrane, preterm labor, placenta previa), other medical disease (diabetic mellitus) and severe preeclampsia that need urgent termination. 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) .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  $<100,000/cm^3$ , all were excluded.

## Methods

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 to detect hypertension, heart diseases, chest diseases or other medical disorders. Transabdominal ultrasound for assessment of fetal wellbeing was done. Laboratory investigations including; complete blood picture, fasting and postprandial blood sugar, liver function tests, renal function test and serum uric acid assay.

Serum uric acid assay was done with kits code41, 000 – spineract. The principle of the test was that Uric acid is oxidized by uricase to allantoin and hydrogen peroxide (2H<sub>2</sub>O<sub>2</sub>), which under the influence of POD, 4-aminophenazone (4-AP) and 2-4 Dichlorophenolsulfonate (DCPS) forms a red quinoneimine compound



The intensity of the red color formed is proportional to the uric acid concentration in the sample.

### Grouping

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

Follow up of maternal outcome and fetal outcome were done.

### RESULTS

Demographic data of three studied groups showed no statistically significant of age and gestational age.

There were statistically significant increase of serum uric acid, urea and creatinine in high group compared to middle and low ones.

The study outcome showed there were 79 fetuses with good outcome (79%), (28 fetuses from the low group, 26 from the middle group and 25 from the high group), and 21 fetuses with bad outcome (intrauterine growth restriction (IUGR), Stillbirth, neonatal intensive care unit (NICU) and preterm baby) (21%), (4 fetuses from the low group, 2 fetuses from the middle group and 15 fetuses from the high group). Bad fetal outcome is directly proportionate to the serum uric acid level, percentage in high group is (37.5%) from all fetuses of this group, comparing with the low group (12.5%) and (7.1%) of the middle group. There was no complication in low-level uric acid mothers, while complicated cases in middle group were (17.1%) and (37.5%) in high group. Eclamptic cases were (7.1%) in middle group and (15%) in high group. Accidental hemorrhage presented in only (5%) of high group, HELLP syndrome was in (7.5%) of high group, acute renal failure in (5%) of high group and intensive care unit admission (ICRU) in high group was (5%). More complications were observed in high uric acid serum level associated with pregnancy induced hypertension and the results were significant (*p* value=0.015) (Tables 1, 2, and 3).

**Table 1. Biochemical Parameter of the Three Studied Groups**

		Range	Mean±S. D	F. test	p Value		
Uric acid	Low	2.4 – 3.5	3.14±0.28	471.087	0.001*	P1	0.001*
	Middle	3.8 – 4.2	4.03±0.12			P2	0.001*
	High	6 - 9	7.39±0.94			P3	0.001*
Urea	Low	20 – 33	26.09±4.55	90.317	0.001*	P1	0.135
	Middle	25 – 35	28.93±3.69			P2	0.001*
	High	25 – 70	47.25±10.28			P3	0.001*
Creatinine	Low	0.5 – 0.8	0.69±0.09	40.686	0.001*	P1	0.644
	Middle	0.5 – 0.9	0.68±0.13			P2	0.001*
	High	0.5 – 1.3	0.97±0.21			P3	0.001*

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      P3: Middle & High

**Table 2. Fetal Outcome in Three Studied Groups**

	Fetal outcome		Low	Middle	High	Total
Good	N		28	26	25	79
	%		87.5%	92.9%	62.5%	79.0%
Bad	N		4	2	15	21
	%		12.5%	7.1%	37.5%	21.0%
Total	N		32	28	40	100
	%		100.0%	100.0%	100.0%	100.0%

Chi-square  $\chi^2$  11.203  
p Value 0.004\*

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 in Studied Groups**

Maternal outcome		Low	Middle	High	Total
No complications	N	32	26	25	63
	%	100.0%	92.9%	62.5%	63.0%
Eclampsia	N	0	2	6	7
	%	.0%	7.1%	15%	7.0%
Accidental hemorrhage	N	0	0	2	7
	%	.0%	.0%	5%	7.0%
HELLP	N	0	0	3	15
	%	.0%	.0%	7.5%	15.0%
ICRU	N	0	0	2	5
	%	.0%	.0%	5%	5.0%
ARF	N	0	0	2	3
	%	.0%	.0%	5%	3.0%
Total	N	32	28	40	100
	%	100.0%	100.0%	100.0%	100.0%
Chi-square	$\chi^2$	22.001			
	<b>p Value</b>	0.015*			

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

## DISCUSSION

Gestational hypertension is a medical disorder worldwide that complicates approximately 12-22% of the pregnancies.<sup>16</sup> Preeclampsia is defined as the development of hypertension, proteinuria, or both after 20 weeks in a woman with previously normal blood pressure. Elevated uric acid is a component of preeclampsia syndrome that was recognized many years ago. Not only the hypertensive disorders in pregnancy are linked with elevated serum uric acid, but also the essential hypertension is associated with the abnormalities in the levels of serum uric acid and lipid profile. 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 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> trimester of pregnancy respectively.<sup>17</sup> Women with gestational hypertension and hyperuricemia have evidence of endothelial dysfunction and deliver growth-retarded babies.<sup>18</sup>

In our study 100 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 (25.44±2.15), (26.18±2.02) for the middle group and (26.40±4.67) for the high group and there was no significant difference between the three groups ( $p=0.470$ ). The mean gestational age for the low group was (35.41±2.01), (35.68±1.33) for the middle group and (35.40±1.66) for the high group. There was no significant difference between the mean of the three groups ( $p=0.768$ ).

Anela Khaleeq et al.<sup>19</sup> 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.

In our study, the first group with uric acid below 25<sup>th</sup> percentile (low group, <3.7 mg/dL), Systolic blood pressure with mean (141.25±3.36) diastolic blood pressure with mean (90.63±2.46) .

The second group with uric acid from 25<sup>th</sup> to 75<sup>th</sup> percentile (middle group, 3.8 to 5.7 mg/dL). Systolic blood pressure with mean 145±5.09 and diastolic blood pressure with mean 92.86±4.60.

The third group with Uric acid above 75<sup>th</sup> percentile (high group, >5.8 mg/dL). Systolic blood pressure with mean 170.25±8.00 and diastolic blood pressure, with mean 170.25±5.06. There was significant difference in systolic and diastolic blood pressure between the 3 groups.

Also, Kaur P et al.<sup>20</sup> showed that systolic as well as diastolic blood pressure levels in preeclamptic women (150.8±8.6 mmHg, 101.3±8.01 mmHg) are much higher than that of normal pregnant women (114.3±8.6 mmHg, 74.4±6.9 mmHg). This difference is found to be very highly significant ( $p=0.0001$ ). It is also observed that uric acid level is within moderate increase range in 58% patients of study group (preeclamptic group) and 84% patients of 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 high than that of control group i.e. (4.1±1.05 mg%) and this difference is statistically significant ( $p=0.0001$ ).

In our study, urea and creatinine is significantly elevated in high group compared to middle and low group. The mean value of urea in low group is (26.09±4.55), middle group is (28.93±3.69) and in high group is (47.25±10.28). The mean of creatinine in low group is (0.69±0.09), in middle group is (0.68±0.13) and in high group is (0.97±0.21).

Also, Apeksha Niraulaet and his colleagues found that,<sup>22</sup> Serum uric acid was significantly higher in the PIH group (5.46±1.51) compared to the control group (4.03±0.69). On other hand the serum creatinine and urea were approximately similar in between the groups serum creatinine in PIH group (0.50±36) and in control group (0.49±0.14), urea in PIH group (15.77±6.35) control group (15.28±4.70).

Escudero et al,<sup>23</sup> agree 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.

In this study 79 (79%) fetuses had good outcome, (28 fetuses from the low group, 26 from the middle group and 25 from the high group), and 21 fetuses had bad outcome (21%), (4 fetuses from the low group, 2 fetuses from the middle group and 15 fetuses from the high group) are 5 IUGR, 2 still births, 5 NICU, 3 preterm. Bad fetal outcome is directly proportionate to the serum uric acid level. In high group it is (37.5%) compare to (12.5%) of the low group and (7.1%) of the middle group with *p* value (0.004). These results are comparable to those of AU Hosna et al<sup>21</sup>, who classified 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 outcome 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,<sup>19</sup> shows serum uric acid level measurement is a useful and inexpensive marker for predicting preeclampsia and fetal growth retardation in women suffering with 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,<sup>24</sup> 59 women gave birth to a small for gestational age (SGA) neonate (birth weight <10<sup>th</sup> 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 singleton 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,<sup>25</sup> 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 the study conducted by J. Dhaka et al,<sup>26</sup> the relationship of high blood uric acid in pre-eclamptic 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 normo-uricemic 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 hyperurecemia than women with low uric acid level. None of low-level uric acid mothers were complicated, while complicated cases in middle group were (17.1%) and (37.5%) in high group. Eclamptic cases were (7.1%) in middle group and (15%) in high group. Accidental hemorrhage presented in only (5%) of high group, HELLP syndrome was in (7.5%)of high group, acute renal failure in (5%) of high group and intensive care unit admission (ICRU) in high group was (5%) More complications were observed in high uric acid serum level associated with pregnancy induced hypertension and the results were significant (*p*=0.015).

These results are comparable to those of Kondareddy T et al,<sup>25</sup> Who show 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,<sup>27</sup> 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.

## CONCLUSION

Our data reinforce the general agreement about the utility of hyperuricemia in the prognosis of adverse perinatal outcomes in pregnancy induced hypertension. Serum uric acid level measurements are a useful and inexpensive marker for predicting adverse perinatal outcomes.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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