

## Hyperuricemia and Adverse Pregnant Outcomes in Ghanaian Women: Potential Mechanism

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### Abstract

**Background:** Hyperuricemia has been associated with pre-eclampsia (PE) but limited data exist on the potential mechanism for the association. It is therefore imperative that data is collated for the pathogenic role of urate in PE; hence the focus.

**Aim:** To investigate the association between uric acid levels and pregnancy outcomes in Ghanaian women.

**Methodology:** The nested case control study was located at the Obstetrics and Gynecology department of the Korle-Bu Teaching Hospital (KBTH). One hundred and fourteen consented subjects were recruited after ethical clearance was obtained and structured questionnaire administered to them. Four milliliter (4 ml) blood and five milliliter (5 ml) urine samples were taken for biochemical analysis and urinalysis respectively. An automated chemistry analyzer was used to quantify blood chemistry. The data was captured as protected health information (PHI) and analyzed with SPSS version 18.

**Results:** In pre-eclampsia, patients with hyperuricemia (>360  $\mu\text{mol/L}$ ) were associated with low birth weight (1033.3  $\pm$  57.7). Among the pregnant women with lesser weeks of gestation (< 34 weeks), PE patients had their uric acid levels elevated, Apgar scores decreased and birth-weight decreased compared to  $\geq$  34 weeks gestation category.

**Conclusion:** Increased uric acid levels could generate free radicals that might impair the endothelial system and cause adverse pregnant outcomes.

### Introduction

Uric acid is a danger signaling [1] molecule generated from tissue injury, inflammatory cell death, programmed necrosis and or abnormal metabolism. In such states, uric acid activates macrophages and dendritic cells through pattern recognition receptors [2-4] or indirectly through tissue damage and homeostatic perturbations (from inflamed tissue e.g. decreased pH and hypoxia) resulting in the increment of cytokines and chemokines. Cytokines and chemokines sustain the inflammatory response needed to recruit secondary mediators like leucocytes or white blood cells (WBC) and neutrophils for innate immunity [5,6].

A good example of a damaged tissue could possibly distort the genetic composition which is composed of sugar, pyrimidines and purines. Uric acid, a by-product of purine catabolism, is degraded by hepatic enzyme, uricase [7-17]. The normal range for urate in females is 140 – 360  $\mu\text{mol/L}$ . This level varies significantly in humans as a result of factors that decrease excretion or increase generation. Alcohol, low water consumption, high-purine foods consumption and poor exercise are contributing factors to hyperuricemia (high uric acid levels).

The association of hyperuricemia with hypertension has since been recognized by early investigators [7-15,18], suggesting that uric acid might play a pathogenic role in hypertension mediated by several mechanisms such as inflammation, vascular smooth muscle cell proliferation, endothelial dysfunction, activation of the renin – angiotensin – aldosterone system and oxidative stress [19-21].

Other factors may also contribute to why uric acid is associated with hypertension, including alcohol abuse, lead intoxication, obesity and insulin resistance, and diuretic use [22,23]. Lactate has also been known to block urate secretion in the proximal tubes whereas ischemia results in increased uric acid synthesis. According to Sonne et al., [24],

lactate, pyruvate and acetate are precursors of uric acid. The conversion of lactate to pyruvate is catalyzed by lactate dehydrogenase (LDH). Elevated levels of LDH indicate cellular death and leakage of the enzyme from the cell [25]. High levels of LDH have also been found to be associated with severe pre-eclampsia in a limited number of studies [26,27]. LDH isozymes and hyperuricemia still remain implicated in cardiovascular disorders [28].

In ischemia, hyperuricemia [29] as well as oxidant formation [30,31] occurs when ATP is degraded to adenine and xanthine. The finding that ischemia results in an increment of uric acid levels may also account for why uric acid levels increases in pre-eclampsia.

Pre-eclampsia (PE) is a pregnancy – related disease with altered vascular reactivity that leads to hypertension in mother and metabolic alteration of fetus [32]. It is a major public health concern complicating 5% to 7% of all pregnancies [33,34] and causing significant maternal and perinatal morbidity and mortality. PE is therefore a multisystem [35] and multifactorial disorder with no specific identifiable etiology. Numerous methods have been used to predict the onset of PE with

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**Received:** March 22, 2016; **Accepted:** May 21, 2016; **Published:** May 24, 2016

**Citation:** Ababio GK, Adu-Bonsaffoh K, Botchway F, Abindau E, Quaye IKE (2016) Hyperuricemia and Adverse Pregnant Outcomes in Ghanaian Women: Potential Mechanism. Biochem Anal Biochem 5: 275. doi:10.4172/2161-1009.1000275

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varying degrees of efficiency [36-38]. These methods have used fetal/placental and maternal markers in different stages of pregnancy in order to predict the disease. However, impaired endothelial dysfunction [39] and genetic predisposition have been cited as possible pathogenic pathways. In this study, hyperuricemia is envisaged to play a role in this pathogenic pathway. Based on the fact that uric acid is produced during tissue or vessel injury, we hypothesized that crystals of uric acid formed at sites of blood vessel injury is a danger molecule that could elicit inflammation in PE patients causing low birth-weight, hence the focus.

## Aim

To investigate the mechanism and association between uric acid levels and pregnancy outcomes in Ghanaian women.

## Methods

**Anthropometry:** A questionnaire for clinical information was obtained after informed consent and ethical review (MS-Et/M.3 – P.3.2/2013 – 2014) for this nested case-control study situated at the Obstetrics and Gynecology unit, Korle-Bu teaching hospital, Accra. The sample consisted of 130 participants; fifty controls, fifty pregnant normotensives and thirty PE. Subjects that did not complete the entire study and were lost to follow up were made up of one pregnant normotensive, ten controls and 5 PE. In all, one hundred and fourteen (114) completed the study.

**Body mass index:** Weights and heights were obtained and computed for body mass index (BMI). At risk for overweight was defined using the international body mass index (BMI) cutoff points by the World Health Organization's (WHO) International Obesity Task Force [40].

**Dependent variable:** Uric acid levels

**Independent variables:** Body mass index (BMI), Age, blood pressure, lactate dehydrogenase, week of gestation, birth-weight, Apgar scores and full blood count (FBC).

**Inclusion and exclusion criteria:** Only patients diagnosed with PE were recruited after obtaining their consent as cases. Control subjects will include normotensive pregnant and non-pregnant women who gave informed consent were included in the study. Patients with a history of chronic hypertension, renal disease, diabetes, urinary tract infection, cardiovascular disease, multiple pregnancy, molar pregnancy, thyroid dysfunctions and infectious diseases were excluded.

**Blood collection and processing:** Four milliliter (4 ml) blood was drawn from an antecubital vein by means of a plastic syringe and dispensed into EDTA (for FBC) and gel tubes taking careful precautions. Sysmex hematological auto analyzer was used to quantify

FBC whilst RANDOX auto analyzer was used for the determination of LDH and uric acid levels.

**Urinalysis:** Five milliliter spot urine was obtained to determine proteinuria and to categorize subjects into normotensives and PE.

**Blood pressure measurements:** Omron BP monitor was used to determine hypertensives and to group patients into cases and controls.

For the purposes of this study, PE was defined based on American College of Obstetricians and Gynecologist criteria. Accordingly, PE is defined as diastolic blood pressure of  $\geq 90$  mmHg and or systolic blood pressure of  $\geq 140$  mmHg with proteinuria 100 mg/dl in a random urine sample and  $\geq 300$  mg/dl in 24-hr urine sample occurring after 20 weeks of gestation [41,42].

## Data management

As part of data management, the physical integrity of patient records, ethics, data protection were taken into consideration. Data were created on a spreadsheet, corrected for errors, three (3) different backups created and SPSS version 18 used for analysis.

## Results

The study was completed by 114 subjects (Table 1). The ratio of pregnant normotensives to controls to PE was 2:2:1 respectively. The average blood pressure (BP) for pre-eclamptic patients (from their folders) at diagnosis was 148/93 mmHg. Nevertheless, as at the time of recruitment, their BP was still being monitored. BP readings used in this study was the measurement taken as at the time of sampling which seemed to fluctuate.

Significant difference between age, uric acid, lactate dehydrogenase (LDH), white blood cells (WBC), neutrophils (neu%), and hemoglobin levels were observed (Tables 1 and 2). However, when stratified by the weeks of gestation, uric acid, birth-weight and Apgar scores became statistically significant (Table 3). Logistics regression (Supplementary Tables B1 - B1.2), log-linear analysis (Supplementary Tables C1 - C1.2; Supplementary Figures C1 - C1.2) and cross tabulation (Table 2, Supplementary Tables A1 - A2.1) also showed unique patterns. Univariate analysis gave a significant Levene's statistics for LDH, WBC, BMI and age with uric acid being the dependent variable. The hypothesis that hyperuricemia was associated with adverse pregnancy outcomes was also tested (Table 4).

## Discussion

In this study, a report on the association of hyperuricemia and adverse pregnancy outcomes was presented. The study adds unto the existing knowledge elsewhere that the relationship between uric acid

Variable	Pregnant normotensive	Control	Pre-eclampsia	p-value
Age (years)	29.97 ± 5.70 (49)	40.00 ± 10.70 (40)	29.30 ± 5.40 (25)	0.001
BMI (kg/m <sup>2</sup> )	28.90 ± 5.60 (40)	28.40 ± 6.60 (40)	29.00 ± 6.40 (21)	0.523
LDH (U/L)	229.4 ± 74.0 (45)	355.6 ± 179.90 (50)	311.1 ± 245.30 (24)	0.001
Wbc (x10 <sup>9</sup> /L)	7.70 ± 1.80 (49)	5.40 ± 1.50 (50)	9.60 ± 3.60 (18)	0.000
Neu (%)	68.90 ± 6.20 (49)	47.80 ± 8.60 (50)	74.22 ± 9.80 (18)	0.000
Hb (g/dL)	11.10 ± 2.50 (49)	12.81 ± 1.40 (50)	12.20 ± 1.74 (18)	0.000
SBP (mmHg)	108.50 ± 17.90 (48)	120.80 ± 18.40 (37)	95.00 ± 15.10 (13)	0.000
DBP (mmHg)	70.70 ± 13.30 (48)	78.80 ± 11.80 (37)	61.00 ± 13.70 (13)	0.000
Uric acid (μmol/L)	227.70 ± 53.30 (42)	268.20 ± 185.30 (33)	314.30 ± 59.60 (23)	0.018

BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDH = Lactate Dehydrogenase; WBC = White Blood Cells; Neu = Neutrophil; Hb = Hemoglobin

Table 1: Clinical variables in the study.

Cross tab	Significance
Age*ID*BMI	Marginally overweight (p = 0.000)
Age*ID*uric acid	Normal uric acid levels (p = 0.000)
Gestational age*ID*BMI Gestational age*ID*uric acid	See supplementary Table for details

ID = The label for the three (3) categories in the study i.e., pregnant normotensive, control and pre-eclampsia

**Table 2:** Cross tabulation – significant findings seen in these clinical categories only.

	20 ≤ x < 34 weeks			x ≥ 34 weeks		
	Pregnant normotensive	Pre-eclampsia	p-value	Pregnant normotensive Control	Pre-eclampsia	p-value
Age	29.6 ± 3.6 (21)	30.6 ± 5.3 (14)	0.510	29.9 ± 5.5 (21)	26.3 ± 5.8 (11)	0.095
BMI	28.4 ± 4.7 (19)	26.9 ± 2.5 (13)	0.302	28.7 ± 4.9 (14)	32.1 ± 10.6 (7)	0.087
Gestation weeks (from records)	22.5 ± 7.1 (18)	24.6 ± 11.7 (9)	0.566	27.3 ± 7.9 (18)	35.5 ± 0.7 (8)	0.008
Gestation weeks (by interviewer)	27.1 ± 4.5 (18)	28.9 ± 3.2 (15)	0.204	36.7 ± 2.3 (22)	37.7 ± 2.8 (10)	0.295
Birth-weight	2800.0 ± 514.8 (13)	833.3 ± 288.7 (15)	0.001	2970.0 ± 459.6 (10)	3200.0 ± 201.0 (10)	0.164
SBP	107.1 ± 12.2 (21)	86.1 ± 12.5 (6)	0.001	108.2 ± 20.6 (19)	93.3 ± 8.2 (7)	0.078
DBP	68.0 ± 8.1 (21)	55.0 ± 9.6 (6)	0.003	71.8 ± 15.7 (19)	55.0 ± 5.8 (7)	0.000
Uric acid	219.0 ± 41.0 (20)	323.4 ± 33.0 (7)	0.000	250.7 ± 60.0 (17)	288.4 ± 39.0 (11)	0.077
Apgar score (1 min.)	7.5 ± 0.9 (13)	5.0 ± 0.4 (15)	0.000	7.1 ± 1.0 (10)	5.5 ± 2.1 (10)	0.043
Apgar score (5 min.)	8.4 ± 0.9(13)	6.0 ± 0.6(15)	0.000	8.5 ± 0.5(10)	9.0 ± 0.8(10)	0.117

BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

**Table 3:** Clinical variables and pregnancy outcomes sorted out by weeks of gestation.

Uric Acid levels	Birth-weight		
	Pregnant normotensive	Pre-eclampsia	p-value
Normal (140-360µmol/L)	2893.7 ± 505.2 (23)	2116.7 ± 1190.7 (18)	0.007
Increased (>360µmol/L)	-	1033.3 ± 57.7 (5)	-
Decreased (<140µmol/L)	-	-	-

Refer supplementary tables for gestational age categories \* ID \* BMI categories

**Table 4:** Birth-weight sorted out by uric acid levels.

and birth weight in women with pre-eclampsia was concentration dependent [43].

Current literature also suggests that vessel or tissue injury causes inflammation mediated by uric acid. This danger signal [1] modifies the migration and invasion of trophoblast phenotype. This in a way contributes to the inadequate trophoblast invasion and spiral arteriole remodeling [44,45]. The significant finding of uric acid levels in pre-eclampsia (gestational age <34 weeks and ≥ 34 weeks) buttresses the different pathogenic pathways generally described as early-onset and late-onset diseases respectively [46]. Early onset pre-eclampsia is a severe form of the disease with completely different underlying pathophysiology resulting in worse pregnancy outcomes compared with late onset of the disease [47]. We therefore emphasize that hyperuricemia in pre-eclampsia could be attributed to the disease process itself as a secondary effect from significant renal impairment that usually complicate the disease process. Also, increased uric acid production from placental, fetal and maternal tissues through heightened tissues breakdown and/or increased xanthine oxidase activity could possibly explain the increased uric acid concentration thereby leading to endothelial impairment [48,49]. Regular monitoring of the maternal serum uric acid in women with severe pre-eclampsia is therefore recommended in the management of preeclamptic women to help improve the pregnancy outcomes.

Uric acid also prevents superoxide dismutase degradation as noted by Hink et al. [50]. Superoxide dismutase is an enzyme critical in maintaining endothelial and vascular function by catalyzing superoxide anion reactions. These anions or radicals are generated

from the increment of neutrophils that stimulates syncytiotrophoblast microvillous membranes (STBMs) in pre-eclampsia. LDH isozymes e.g. LDH-B is predominant in STBM while LDH-A is immunolocalized in the fetal endothelial system. LDH-A activity increases by 1.6 fold in PE suggesting hypo perfusion to the fetus due to endothelial dysfunction in uteroplacental vessels [51]. It is therefore not surprising to find LDH levels on the rise in this study.

Johnson et al. [43] pointed out that the mechanism by which uric acid impairs the endothelial system remains unknown. However, our findings provide an important insight, whereby, upon activation of macrophage system or dendritic cells by uric acid [1-6], primary mediators (like cytokines or chemokines) elicits the recruitment of secondary mediators (like white blood cells and neutrophils) causing a relatively low birth-weight in PE patients. We therefore stress that any increased oxidant affects placental tissue and fetal nutrition thereby leading to low birth weight.

Also, the increased expression of leukocytes (WBC) and neutrophils seen in this study created inflammatory environ with uric acid as the catalyst that exacerbated inflammation and impaired the endothelial system. Nevertheless, whereas endothelial activation may exist prior to and induce leukocyte activation, there could possibly be a vicious circle in which instance leukocyte activation may in turn further promote endothelial cell activation [52]. Such a local inflammatory response involving enhanced leukocyte-endothelial cell interaction may contribute to the pathogenesis of, and may potentially represent novel targets for therapeutic intervention.

Also, one trigger indicator was the fluctuation of the blood pressure seen in PE patients which could possibly arise from the effects of the danger molecule. It is very possible that other factors like the environment coupled with genetic and or uric acid triggered the effect; but this warrants further investigation.

## Conclusion

Hyperuricemia could generate free radicals that might impair the endothelial system and contribute to the pathophysiology of pre-eclampsia and adverse pregnancy outcomes. Clinical monitoring of uric acid levels in pre-eclampsia and subsequent planned delivery of the fetus based on a specific threshold might improve the obstetric outcomes of pregnancies complicated by this multisystem disorder.

## Acknowledgement

This work was supported by grants from ORID, University of Ghana, Legon. The authors duly acknowledge Mensah J, Tetteh D, Morvey D, Amponsah C, staff of Obstetrics and Gynecology of the Korle-Bu Teaching Hospital, Accra, Ghana; and also, Medical Biochemistry, Univ. of Ghana SBAHS.

## Funding Disclosure

Work from the authors' laboratory was supported by grants from ORID, University of Ghana, Legon.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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