International Journal of Biomedical and Health Sciences
Vol. 6, No. 4 December 31, 2010
Printed in Nigeria

0794-4748/2010 $12.00 + 0.00

http://www.asopah.org

IJBHS 2010167/6416

Plasma uric acid level in overweight and obese pregnant women and its association with adverse pregnancy outcomes

Emmanuel I. Ugwuja*[1] and Boniface N. Ejikeme[2]

[1] Department of Chemical Pathology, Faculty of Clinical Medicine, Ebonyi State University, P.M.B. 053 Abakaliki, Nigeria

[2] Department of Obstetrics and Gynaecology, Faculty of Clinical Medicine, Ebonyi State University Abakaliki, P.M.B. 053, Abakaliki, Nigeria

(Received October 12, 2010; Accepted November 6, 2010)

ABSTRACT: **Background:** Hyperuricaemia, a common lifestyle disorder related to obesity has been associated with adverse pregnancy outcomes. **Objective:** To ascertain the correlates of plasma uric acid in overweight and obese pregnant women and to investigate their association with adverse pregnancy outcomes. **Materials and methods:** Blood collected at recruitment from 349 pregnant women (gestational age ≤ 25 wks) who gave their consent were analysed for uric acid alongside haematological and other biochemical parameters using standard laboratory methods. Maternal sociodemographic/obstetric and anthropometric parameters were obtained by questionnaire while maternal and foetal outcomes were recorded at delivery. **Results:** Plasma uric acid although significantly ($p < 0.05$) higher in the overweight women in comparison to either the obese or women with normal body mass index (BMI), and comparable in obese and women with normal BMI, the morbidly obese pregnant women had uric acid level that was significantly ($p < 0.05$) lower than that found in overweight, obese and women with normal BMI. However no correlation was observed between plasma uric acid and maternal BMI ($r = -0.058$, $p = 0.304$). Both women with normal and elevated plasma uric acid levels had comparable ($p > 0.05$) maternal outcomes, but while preterm delivery was significantly ($p < 0.05$) higher in the latter when compared with the former, low birth weight and still birth were comparable ($p > 0.05$) between the groups. It may therefore be concluded that overweight pregnant women had significantly higher uric acid level than pregnant women of normal BMI with hyperuricaemia associated with preterm delivery.

Key words: Hyperuricaemia, body mass index, pregnancy, hypertension, preterm delivery

Introduction

Uric acid is an inert end product of purine metabolism formed by the action of xanthine oxidase on xanthine and hypoxanthine. It has been found that plasma uric acid correlate positively with plasma adenosine levels (1). Ideally during early pregnancy (first and second trimesters), plasma uric acid concentration falls 25-35 % due to oestrogen (a uricosuric hormone), increased plasma volume, glomerular filtration and fractional excretion, but rises to non-pregnant value by term due to increased foetal production, decreased albumin binding and decreased renal clearance (2, 3). Women with twin pregnancy have been found to have higher serum uric acid level than those with singleton pregnancy (1). Uric acid like other strong reducing agent is a potent antioxidant (4), but at higher level and in compromised antioxidant states, such as reduced ascorbate availability may be pro-oxidant (5). It has been shown that uric acid levels in adults as well as in adolescents are positively correlated with body mass index (BMI) and hyperuricaemia is considered a common lifestyle disorder related to obesity (6). Overweight/obesity is a metabolic state known to be associated with clinical conditions, such as hypertension, cardiovascular and renal diseases (7-11).

Studies have shown that hyperuricaemia is a component of the metabolic syndrome (12-14), which involves combination of abdominal obesity, insulin resistance, hypertension, dyslipidaemia with hypertriglyceridaemia and low high density lipoprotein (HDL), prothrombotic tendencies and increased markers of inflammation (15, 16). Although hyperuricaemia has been consistently observed as one of the earliest signs of preeclampsia with adverse maternal and foetal outcomes, such as still birth and preterm delivery, just to mention but few (17, 18), its role in the pathophysiology of the disease is still being debated (3, 19-21). With increasing weight gain during pregnancy, we hypothesize increased plasma uric acid in overweight and obese pregnant women with attendant adverse pregnancy outcomes. This study therefore seeks to ascertain the correlates of serum uric acid in overweight and obese pregnant Nigerians and to investigate their association with adverse pregnancy outcomes.

Materials and Methods

This study is a part of a larger study that investigated the impact of maternal trace element (copper, iron and zinc) status on pregnancy outcomes. The study was carried out in Abakaliki, the capital of Ebonyi State in the South Eastern Nigeria at the Department of Obstetrics and Gynaecology of the Federal Medical Centre Abakaliki. Federal Medical Centre Abakaliki is one of the tertiary health facilities in the region. The Ethics and Research Committee of the Institution approved the protocol for this study. The study population comprised 349 pregnant women receiving antenatal care at the Hospital. Inclusion criteria include , having uncomplicated singleton pregnant at gestational age ≤ 25 weeks (based of date of last menstrual period/ultrasonography, resident in Abakaliki and environs, and free from underlying chronic diseases. Women excluded from the study were those seropositive for HIV I/II and those with multiple pregnancies. After obtaining their consents, structured questionnaire was administered to each participant to obtain sociodemographic/obstetric data such as age, parity, occupation, literacy level, living accommodation, tobacco smoking and alcohol consumption habits.

Maternal pre-pregnancy BMI (Kg/m2) was calculated from the weight (Kg) and height (cm). The women were grouped into four BMI categories as reported by Bhattacharya et al. (7) as follows:

Categories	BMI (Kg/m^2) values
Normal	20-24.9
Overweight	25-29.9
Obese	30-34.9
Morbidly obese	>= 35.0

Five millilitres (5ml) of venous blood was collected once at recruitment between 08.00-10.00 hour and dispensed into heparinised bottles (3.0ml) and EDTA bottles (2.0ml) respectively. The plasma was isolated by centrifuging the heparinised blood at 2000g for 5 minutes and frozen until analysis. Participants were followed-up regularly; based on appointment with their Consultants till delivery. At every follow-up, participants were evaluated by the attending Obstetricians for concomitant illness such as diabetes (fasting plasma glucose > 7.8 mmol/l), malaria (positive malaria parasite on thick/thin smear), upper respiratory tract infection (URTI; presence of cough and catarrh), urinary tract infection (UTI, positive urine protein, nitrite and leucocytes), hypertension (blood pressure > 140/90 mmHg) and anaemia (haemoglobin concentration < 11.0 g/dl). At delivery, baby's birth outcomes such as preterm delivery (gestational age at delivery ≤ 37 weeks), low birth weight (birth weight < 2.5 Kg), and still birth, were recorded by the attending midwives.

Laboratory analyses

Maternal haematocrit (HCT), haemoglobin concentrations (HBC) and total white blood cell counts (TWBC) were determined as described previously (22), plasma albumin was determined by colorimetric bromocresol green (23) methods as described previously, while uric acid was determined by uricase method as described by Fossati *et al.* (24). Hyperuricaemia is defined as plasma uric acid of > 350 µmol/l (25)

Data analysis

The data collected were analysed using Statistical Package for Social Science (SPSS version 10). Data were analysed for mean and standard deviation. On- way ANOVA was used to test for differences in means and value of $p \leq 0.05$ was considered significant.

Results

From Table 1, while maternal haematocrit was significantly ($p < 0.05$) higher in overweight and obese (including morbidly obese) women in comparison to women with normal body mass index (BMI), and higher in morbidly obese women than overweight and obese women, it was comparable ($p > 0.05$) between overweight and obese women. Although total white blood cell counts was not statistically ($p > 0.05$) different among the BMI groups, haemoglobin concentration though was found to be significantly ($p < 0.05$) higher in overweight and obese women when compared to their counterparts with normal BMI, it was comparable ($p > 0.05$) between overweight and obese groups. However, albumin concentrations were comparable among the groups. For plasma uric acid, although significantly ($p < 0.05$) higher level was observed in the overweight women in comparison to either the obese or women with normal BMI, and comparable level found in obese and women with normal BMI, the morbidly obese pregnant women had uric acid level that was significantly lower than that found in overweight, obese and women with normal BMI.

Except for plasma uric acid concentration which was significantly ($p < 0.05$) higher in hyperuricaemic than normal women, both groups had comparable ($p > 0.05$) age, BMI, gestational age, haematological and biochemical parameters (Table 2). Partial correlation analysis after controlling for age and parity showed that plasma uric acid was not correlated with maternal BMI ($r = -0.058$, $p = 0.304$).

Table 3 shows the maternal and foetal outcomes in relation to maternal plasma uric acid concentration. Although maternal anaemia was higher in hyperuricaemic women in comparison to women with normal uric acid concentration, the incidence of hypertension and concomitant illnesses were higher in the latter, although these were not statistically significant ($0 > 0.05$). However, while preterm delivery was significantly ($p < 0.05$) higher in the hyperuricaemic women when compared with women with normal uric acid level, low birth weight and still birth were comparable ($p > 0.05$) between the groups , although there appeared to be higher prevalence of the two adverse foetal outcomes in women with normal uric acid concentration.

Table 1: Maternal haematological and biochemical parameters in relation to maternal BMI[1,2]

Maternal parameters	Maternal BMI groups			
	Normal (n = 142)	Overweight (n = 124)	Obese (n = 60)	Morbidly obese (n = 19)
Haematocrit (%)	29.54 ± 3.57	30.73 ± 4.35[a]	30.68 ± 3.92[a]	31.68 ± 2.68[b]
Haemoglobin (g/l)	9.94 ± 1.25	10.63 ± 2.35[a]	10.29 ± 1.39[a]	10.62 ± 0.9[a]
WBC (x 10^{-9})	5.73 ± 1.52	5.55 ± 1.40	5.59 ± 1.37	5.23 ± 1.50
Albumin (g/l)	3.50 ± 0.77	3.38 ± 0.80	3.50 ± 0.82	3.49 ± 0.84
Uric acid (µmol/l)	326.97 ± 114.55	517.42 ± 115.81[a]	325.82 ± 105.16[b]	306.78 ± 95.74[c]

[1]Values are expressed as Mean ± S.D.
[2] Values carrying different superscripts horizontally are significantly ($p < 0.05$) different.

Table 2: Maternal Characteristics in Relation to Plasma Uric Acid Levels [1]

Parameters	Normal (n = 271)	Hyperuricaemic (n= 78)	p-values
Age (yrs)	27.1 ± 4.6	26.8 ± 5.3	0.557
BMI (Kg/m^2)	27.3 ± 4.3	27.2 ± 4.1	0.805
Gestational age (Wks)	21.7 ± 3.1	27.0 ± 3.1	0.524
Parity (n)	1.5 ± 1.5	1.2 ± 1.4	0.161
Uric acid (µmol/l)	275.6 ± 70.3	501.9 ± 60.0	0.000*
Albumin (g/dl)	3.5 ± 0.8	3.5 ± 0.8	0.756
TWBC (x^9/l)	5.6 ± 1.4	5.8 ± 1.7	0.116
Haemoglobin (g/dl)	10.2 ± 1.2	10.1 ± 1.4	0.522
Haematocrit (%)	30.3 ± 4.0	30.1 ± 4.0	0.629

BMI: Body mass index; **TWBC:** Total white blood cell count
[1] Values are expressed as mean ± standard deviation.
* $p < 0.05$.

Table 3: Maternal and foetal outcomes in relation to maternal plasma uric acid levels [1]

Parameters	Normal	Hyperuricaemic	p-values
Maternal outcomes			
Hypertension	35/267 (13.1)	7/76 (7.9)	0.216
Anaemia	117/271 (43.2)	46/78 (59.0)	0.304
Concomitant illnesses	171/269 (63.6)	40/76 (52.6)	0.332
Foetal outcomes			
Preterm delivery	13/254 (5.1)	9/64 (14.1)	0.014*
Low birth weight	37/254 (14.6)	7/64 (10.9)	0.750
Still birth	11/254 (4.3)	1/64 (1.6)	0.299

[1] Percentage in parenthesis

Discussion

The present study has shown that maternal plasma uric acid, although significantly higher in overweight than in normal or obese pregnant women, was not correlated with maternal BMI. Also, apart from preterm delivery which was significantly higher in hyperuricaemic women, other pregnancy outcomes assessed (both maternal and foetal) were found not to be associated with hyperuricaemia.

Although to the best of our knowledge, no previous study had compared the level of uric acid among different BMI groups in pregnant women, significantly higher plasma uric acid in overweight pregnant women when

compared to obese and normal weight women in the present study needs further evaluation. However, it has been reported (6) that serum uric acid levels of subjects with high percentage of overweight (POW) ≥ 20 % are significantly higher than those of subjects with low POW (< 20 %). In pregnancy, plasma uric acid has been shown to fall during the first and second trimester only to return to the value of non-pregnant states at term (3, 26). Although, it is not clear whether this type of changes are applicable to overweight pregnant women, the present findings suggest either increased production of uric acid or reduced excretion or both (11, 27, 28) .

It has however been suggested that mechanisms other than altered glomerular filtration, such as underlying metabolic syndrome, tissue damage, oxidative stress, and inflammation, may contribute to increased uric acid during pregnancy (3). Although we did not evaluate the renal functions in our subjects, the higher uric acid level in twin pregnancy when compared to singleton pregnancy reported by Suzuki *et al.* (1) however supports increased production as a possible contributor to elevated plasma uric acid observed in overweight pregnant women in the present study. Since overweight pregnant women are most likely to be carrying heavier foetus, we speculate increased contribution from the foetus to maternal uric acid pool (29). It has been shown that macrosomia (birtweight > 4000g) are common in the obese and morbidly obese women respectively, compared to women with normal BMI (7). Regrettably however, hyperuricaemia was neither observed in obese nor in morbidly obese pregnant women. Although the reason for this observation remains obscure, we propose increased plasma volume as a possible cause of lower uric acid in obese and morbidly obese women in comparison to overweight and/or women with normal BMI in the present study as higher BMI been associated with higher plasma volume (30, 31). The lack of correlation between maternal plasma uric acid level and BMI, reported here contrasts a positive correlation reported by Oyama *et al.* (6) in early adolescence. The inconsistency in the findings may be attributed to difference in subjects. However, the confounding effect of obese and morbidly obese subjects included in the analysis cannot be ruled out.

The absence of effects of hyperuricaemia on maternal outcomes, such as anaemia, hypertension and concomitant illnesses recorded in the present study contrast earlier findings (32-35). However, it corroborates the limited utility of uric acid in predicting the occurrence or/and severity of preeclampsia reported by some authors (19, 21). However, significantly higher preterm delivery observed in hyperuricaemic mothers in comparison with their counterparts with normal uric acid levels in the present study corroborates earlier study (18) where preterm births were reported in 20 of the 100 women studied and suggests a role for uric acid in the pathogenesis of the adverse foetal outcome. Although hyperuricaemia has been observed as a constant feature in preeclamptic pregnancy (3, 17, 36), its role in adverse foetal outcomes has not been fully elucidated. However, reports of the roles of uric acid as proinflammatory (11, 37), as inhibitor of endothelial cell proliferation and migration (38) and promoter of endothelial dysfunction and damage (11, 39, 40) suggest its involvement in mediating adverse foetal outcomes, including preterm delivery. Uric acid is a plasma antioxidant capable of scavenging superoxide, hydroxyl radical and singlet oxygen (41) as well as reducing nitrosylation of tyrosine residues on proteins by peroxynitrite and capable of maintaining superoxide dismutase activity (42), a powerful antioxidant enzyme. However, it has been shown that in a state of elevated uric acid and reduced ascorbate concentration; uric acid can become prooxidant and mediates a lot of adverse clinical effects (3, 5). Hence it may be argued that in hyperuricaemic pregnant women, the oxidative stress (3, 4) induced by uric acid in the placenta may be responsible for the higher incidence of preterm delivery recorded in the present study. It may therefore be concluded that overweight (BMI = 25-29.9 Kg/m^2) pregnant women had significantly higher uric acid level than pregnant women with normal BMI (20-24.9 Kg/m^2) and hyperuricaemia is associated with preterm delivery.

References

1. Suzuki, S, Yoneyyama, Y, Sawa, R and Araki, T: Relation between serum uric acid and plasma adenosine levels in twin pregnancies. *Obstet Gynaecol* 2000; 96: 507-10.
2. Davidson JM and Dunlop W: Renal haemodynamics and tubular function in normal human pregnancy. *Kidney Int* 1980; 18 (2): 152-61.
3. Powers, RW, Bodnar, LM, Ness, RB, Copper, KM, Gallaher, MJ, Frank, MP, Daftary, AR and Roberts, JM: Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricaemia at delivery. *Am J Obstet Gynaecol* 2006; 194: 160.e1-160.e8.
4. Becker BF: Towards the physiological function of uric acid. *Free Radic Biol Med* 1993; 14: 615-31.
5. Abuja PM: Ascorbate prevents prooxidant effects of urate in oxidation of human low density lipoprotein. *FEBS Lett* 1999; 446: 305-8.

6. Oyama C, Takahashi T, Oyamada M, Oyamada T, Ohno T, Miyashita M, Saito S, Komatsu K, Takashina K and Takada G: Serum uric acid as an obesity-related indicators in early adolescence. *Tohoku J Exp Med* 2006; 209: 257-262.
7. Bhattacharya S, Campbell DM, Liston WA, Bhuttacharya S: Effect of body mass index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health* 2007; 7: 168.
8. Smith GCS, Shah I, Pell JP, Crossley JA, Dobbie R: Maternal obesity in early pregnancy and risk of spontaneous and elective preterm deliveries: A retrospective cohort study. *Am J Public Health* 2007; 97 (1): 157-162.
9. Rode L, Nilas L, Wojdemann K, Tabor A: Obesity-related complications in Danish single cephalic term pregnancies. *Obstet Gynaecol* 2005; 105: 537-542.
10. Kristensen J, Vestergaard M, Wisborg K, Kesmodel U, Secher NJ: Prepregnancy weight and the risk of stillbirth and neonatal death. *BJOG* 2005; 112: 403-408.
11. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S *et al:* Is there a pathogenic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; 41: 1183-90.
12. Robinson R: The foetal origins of adult disease no longer just a yhpothesis and may be critically important in south Asia. *BMJ* 2001; 322: 375-6.
13. Solomons NW: Program and policy issues related to promoting early nutritional influences to prevent obesity, diabetes, and cardiovascular disease in later life: a developing countries view. *Matern Child Nutr* 2005; 1: 204-15.
14. Grundy SM, Cleeman J, Daniels SR, Donato KA, Eckel RH, Franklin BA *et al:* Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement: Executive summary. *Circulation* 2005; 112: e285-e90.
15. Grundy SM, Cleeman J, Daniels SR, Donato KA, Eckel RH, Franklin BA *et al:* Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Curr Opin Cardiol* 2006; 12: 1-6.
16. Bitsori M and Kafatos A: Dymetabolic syndrome in childhood and adolescence. *Acta Paediatrica* 2005; 94: 995-1005.
17. Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB *et al:* uric acid is as important as proteinuria in identifying foetal risk in women with gestational hypertension. *Hypertension* 2005; 46: 1263-9.
18. Hosna AUI, Bhuiyan AKMB, Ferdous NE, Ahmed MK, Siddique MA, salman M, Begum SR, Rahman MM and Ahsan MR: Effect of hyperuricaemia in Perinatal outcomes in hypertensive disorder of pregnancy. *University Heart Journal* 2008; 4 (2): 36-40.
19. Cnossen J, Ruyter-Hanhijarvi H, Van der Post JAM, Mol BWJ, Khan KS and Riet GT: Accuracy of serum uric acid determination in predicting pre-eclampsia: a systemic review. *Acta Obstet Gynaecol* 2006; 85: 519-525.
20. Weerasekera DS and Peiris H: The significance of serum uric acid, creatinine, and urinary microprotein levels in predicting pre-eclampsia. *J Obstet Gynaecol* 23 (1): 17-19.
21. Lim, KH, Friedman, SA, Ecker, JL, Kao, L and Kilpatricbk, SJ: The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. *Am J Obstet Gynaecol* 1998; 178: 1067-71.
22. Dacie, J. V. and Lewis, S. M: Practical Haematology, 8th Ed. Churchill livingstone, Edinburg 1994; Pp 49-59.
23. Hill, P.G: The measurement of albumin in serum and plasma. *Ann. Clin. Biochem* 1985; 22: 565-578.
24. Fossati P, Prencipe L and Berti G: Use of 3, 5- dichloro-2-hydroxybenzenesulfonicacid/4-aminophenazone chromogenic system in direct enzymic assay of uric acid in serum and urine. Clin Chem 1980; 26: 227-231.
25. Tietz NW: Clinical guide to laboratory tests 2nd edition, Saunder Co 1991.
26. Lind T, Godfrey KA, Otun H and Philips PR: Changes in serum uric acid concentrations during normal pregnancy. *Br J Obstet Gynaecol* 1984; 91: 128-32.
27. Many A, Hubel CA and Roberts JM: Hyperuricaemia and xanthine oxidase in preeclampsia, revisited. *Am J Obstet Gynaecol* 1996; 174: 288-91.
28. Conrad KP and Lingheimer MD: Renal and cardiovascular alterations. In: Lindheimer MD, Roberts JM, Cunningham FG ed. Chesley's hypertensive disorders in pregnancy. Samford (CT): Appleton and Lange; 1999.
29. Fischer RL, Bianculli KW, Hediger ML and Scholl TO: Maternal serum uric acid levels in twin gestation. *Obstet Gynaecol* 1995; 85: 60-4.
30. Raison J, Achimastos A, Bouthier J, London G and Safar M: Intravascular volume, extracellular fluid volume, and total body water in obese and nonobese hypertensive patients *Am J Cardiol* 1983; 51 (1): 165-170.
31. Bañez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, Wang Y, *et al.*: Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA. 2007; 298(19): 2275-80.
32. Conrad KP and Lingheimer MD: Renal and cardiovascular alterations. In: Lindheimer MD, Roberts JM, Cunningham FG ed. Chesley's hypertensive disorders in pregnancy. Samford (CT): Appleton and Lange; 1999.
33. Heinig M and Johnson RJ: Role of uric acid in hypertension, renal dis ease, and metabolic syndrome. *Cleve Clin J Med* 2006; 73 (12): 1059-64.
34. Acicn, P, Lloret, G and Lloret, M; Perinatal morbidity and mortality in pregnancy hypertensive disorders: prognostic value of the clinical and laboratory findings. *Int J Gynaecol Obstet* 1990; 32: 229-35.
35. Sagen, N, Kjell, H and Nilsen, S: Serum urate as a predictor of foetal outcomes in severe preeclampsia. *Acta Obstet Gynaecol Scand* 1984; 63: 71-5.
36. Bainbridge, SA and Roberts, JM: Uric acid a prognostic factor in preeclampsia. *Placenta* 2008; 22 (Sppl.): S67-S72.

37. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T *et al:* Uric acid stimulates monocyte chemoattractant protein-1 production in vasculat smoothe muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 2003; 41: 1287-93.
38. Kang DH, Park SK, lee IK and Johnson RJ: Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol* 2005; 16: 3553-62.
39. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M *et al:* A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 2002; 13: 2888-97.
40. Kang DH, Finch J, Nakagawa T, Karumanchi SA, Kanellis J, Granger J, *et al:* Uric acid, endothelial dysfunction and preeclampsia: serching for a pathogenic link. *J hypertens* 2004; 22: 229-35.
41. Simic M and Jovanovic S: Antioxidation mechanism of uric acid. *J Am Chem Soc* 1989; 111: 5778-82.
42. Hink HU, Santanam N, Dikalov S, Mccann L, Nguyen AD, Parthasarathy S, *et al:* Peroxidase properties of extracellular superoxide dismutase: role of uric acid in modulating *in vivo* activity. *Arterioscler Thromb Vasc Biol* 2002; 22: 1402-8.