Int J Biol Med Res. 2011; 2(1): 390-393

BioMedSciDirect Publications

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International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original Article

Study of uric acid and nitric oxide concentrations in preeclampsia and normal pregnancy

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ARTICLE INFO

Keywords:
Pregnancy-induced hypertension (PIH),
Vasopressor,
Vasodilator,
Nitric oxide.

ABSTRACT

Preeclampsia is a pregnancy specific multisystemic syndrome and a leading cause of maternal and fetal morbidity and mortality. The study comprised of 30 normal and 30 preeclampsia cases in their third trimester of pregnancy and the following estimations were done: Serum and urine uric acid, plasma nitric oxide (NO), urine pH, urine creatinine. There was an increase in both serum and urine uric acid levels in the cases (P = 0.000), though the urinary pH in both the groups were similar (P = 0.4). Urinary creatinine in both groups was not different. Plasma nitric oxide in the preeclampsia cases was significantly low (P = 0.000) as compared to controls. It was about one third the levels obtained in controls. There was a negative correlation of systolic BP with plasma NO levels in controls and positive in cases. As pregnancy progressed there was a decrease in plasma NO levels in both cases and controls. Urine uric acid to creatinine ratio increased with the decrease in NO levels and can be used as a marker for preeclampsia.

1. Introduction

Preeclampsia is a pregnancy specific syndrome and a leading cause of maternal and fetal morbidity and mortality [1]. It is a complex multisystemic syndrome and far more than simply gestational hypertension and proteinuria [2]. Increased serum uric acid levels in preeclampsia though reported 80 years ago [3] has been actively debated [4]. Nitric oxide (NO) is generated by endothelial type II nitric oxide synthase (NOS) and acts as a vasodilator. During pregnancy NO is one of the most important relaxing factors for myometrium and also in the control of blood flow in uterus and placenta [5]. However studies have shown controversial reports in preeclampsia. Some have reported an increase [5] and others have reported a decrease [6] in NO levels in preeclampsia. The focus of our current study was to determine the serum uric acid and nitric oxide levels in preeclampsia and compare it with the levels obtained in controls comprising of normal pregnant women.

2.Material and Methods

The departments of Biochemistry and Obstetrics and Gynecology, Pondicherry Institute of Medical Sciences, Pondicherry, jointly carried out the present study. Informed consent was taken from all individual subjects inducted into the study. The study comprised of 30 normal healthy pregnant women and 30 pre- eclampsia cases attending antenatal OPD or labor room in their third trimester of pregnancy.

The diagnosis of preeclampsia was based on the definition of American College of Obstetrics and Gynecologists [7].

1) Systolic blood pressure greater than 140 mm Hg or a rise of at least 30 mm Hg or

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2) Diastolic blood pressure greater than 90 mm Hg or a rise of at least 15mm Hg (manifested on two occasions at least 6 hours apart) and

3) Proteinuria of 300 mg or greater in 24 hours urine collection or protein concentration of 1gm/L (on two occasions of at least 6 hours apart)

I**nclusion criteria (1) Cases:** Primigravida with diagnosed preeclampsia with an age ranging from 18- 35 years. (2) Controls: Primigravida with normal BP, no proteinuria and without any other systemic or endocrine disorder. They were age matched with the cases. All subjects included were in their third trimester (gestational age of 24 weeks).

Exclusion criteria: included diabetes mellitus with or without treatment, obesity, severe anemia (Hb < 6 gm%) or subjects suffering from any other systemic or endocrine disorder. Patients with eclampsia were also excluded as they will be given only IV glucose and will not be on normal diet.

Blood samples and urine samples were collected from all subjects and the following biochemical parameters were estimated.

1. Serum and urine uric acid using the uricase peroxide method [8].
2. Plasma nitric oxide using the Greiss reaction [9].
3. Urine creatinine by 1 in 10 dilution using the kinetic Jaffe reaction [10]
4. Urine pH was measured in a pH meter

Uric acid and creatinine levels were analyzed in the auto analyzer – Dimension AR RMT, Dade Behring limited, UK using the reagent kit provided.

Data were statistically analyzed by students T test and Pearson's correlation and expressed in terms of P value. P of < 0.05 was considered statistically significant.

3 Result

The preeclampsia case had elevated systolic and diastolic BP (Table 1) as compared to normal healthy controls (P = 0.000). There was an increase in both serum and urine uric acid levels in the cases (P = 0.000), though the urinary pH in both the groups were similar (P = 0.4). Urinary creatinine in both groups was not different. Plasma nitric oxide in the preeclampsia cases was significantly low (P = 0.000) as compared to controls. It was about one third the levels obtained in controls; cases 3.03 ± 0.96 and controls 8.9 ± 2.26 µmol/l

There was a negative correlation of systolic BP with plasma NO levels in controls and positive in cases. However neither were statistically significant (Table 2). There was an increase in NO levels with increase in diastolic BP in both the groups. In the control groups with increase in gestational age both systolic and diastolic BP decreased and the same increased in the cases but were not statistically significant. As pregnancy progressed there was a decrease in plasma NO levels in both cases and controls. The negative correlation between serum uric acid and plasma NO levels were consistent in both cases and controls (P = not significant). Urinary uric acid: creatinine ratio versus plasma NO levels showed a positive (P value not significant) and negative (P< 0.05) relation in controls and cases respectively.

Table 2. Pearson's Correlation coefficient of Plasma NO levels with various parameters.

Correlation of NO with:	r in controls	r in cases
Systolic BP	- 0.063	0.0287
Diastolic BP	0.034	0.189
Gestational Age	- 0.315	- 0.223
Serum Uric Acid	- 0.056	- 0.232
U. Uric Acid : Creatinine	0.0101	- 0.363*

·P< 0.05

Table 1. General characteristics of cases and controls.

Parameters	Controls	Cases	P
Age (years)	25 ± 3.6	26 ± 4.7	0.3
Systolic BP (mm Hg)	116.55 ± 4.8	136 ± 4.98	0.000
Diastolic BP (mm Hg)	76.67 ± 4.79	90.33 ± 1.83	0.000
Gestational Age (weeks)	35.53 ± 3.1	35.6 ± 3.3	0.936
Hemoglobin (gm/dl)	10 ± 1.7	10 ± 1.6	0.4
Plasma NO (µ mol/ l)	8.9 ± 2.26	3.03 ± 0.96	0.000
Serum Uric Acid (mg/dl)	3.34 ± 1.02	6.33 ± 0.58	0.000
Urine Uric Acid (mg/dl)	25.13 ± 9.78	38.3 ± 12.93	0.000
Urine Creatinine (mg/dl)	63.66 ± 27.25	68.1 ± 26.83	0.528
U. Uric Acid : Creatinine	0.295 ± 0.13	0.78 ± 0.43	0.000
Urine pH	6.03 ± 0.72	6.3 ± 0.73	0.16

Figures 1 and 2 depict the linear regression analysis of plasma NO and serum uric acid levels in cases and controls respectively. Both have a negative correlation: cases, r= -0.23163 and controls, r= -0.0559 which was not statistically significant. The trend lines had different slopes; cases -0.3882 and controls -0.1242, t= 0.63, P > 0.50.

Figure 1. The relationship between serum uric acid and plasma NO in cases.

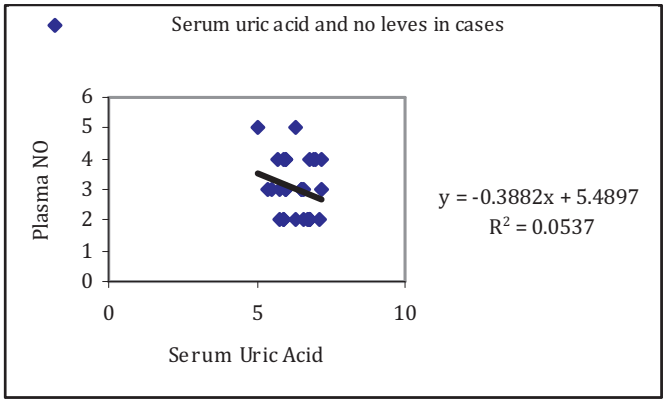
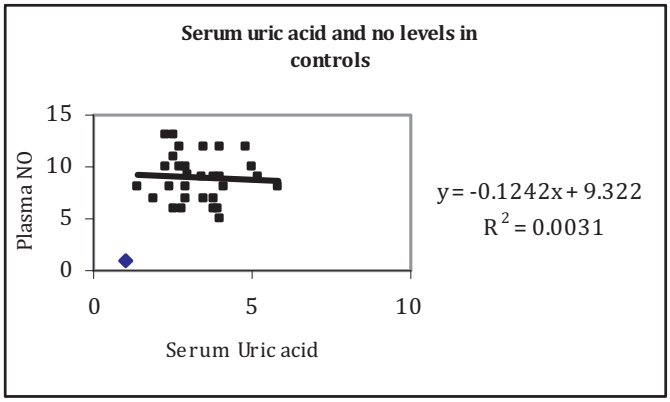


Figure 2. The relationship between serum uric acid and plasma NO in controls.



4.Discussion

NO is related to gestational vasodilatation during pregnancy. Deficiency of or impaired responsiveness to NO has been reported to cause preeclampsia [11]. Preeclampsia is characterized by increased systemic vascular resistance and contracted plasma volume. In parallel, the response to vasopressor agents is exaggerated. It can be assumed that these abnormalities are related to an imbalance in the synthesis of vasoactive agents and that the same is related to endothelial cell damage [12]. As seen in our study, plasma NO levels in preeclampsia fall to one third the levels to that obtained in normal pregnancy and there was also a decrease in plasma NO levels in both cases and controls as pregnancy progressed. Probably suggesting that this change in NO levels could be important in the beginning of delivery and cervical maturation. Pregnancy is characterized by low plasma levels of L-arginine because of increased transfer of amino acids to fetus [13]. Relative deficiency of the precursor in the presence of systolic endothelial damage may cause insufficient synthesis of the product that is NO [11]. To support this hypothesis, it has also been reported that administration of L- arginine ameliorated a syndrome of intravascular coagulation resembling preeclampsia [14] and administration of NO donors and NOS inhibitors provides effective and safe management of complications of preeclampsia [6].

Uric acid is a marker of oxidative stress tissue injury dysfunction and is an independent risk factor for cardiovascular disease [15,16]. During uncomplicated pregnancies serum uric acid concentrations decrease by 25% to 35 % in early pregnancy but then increase throughout pregnancy until towards the end of pregnancy when they approach non pregnant levels [17]. It is proposed that these pregnancy mediated changes in serum uric acid are primarily the result of altered renal handling. Increased serum uric acid in preeclampsia is secondary to reduced renal urate clearance because of renal dysfunction [18] and also due to increased xanthine oxidase activity [19].

It is also possible that increased serum uric acid values may indicate the presence of undiagnosed sub clinical renal disease in some subjects and this may increase the risk for preeclampsia. Increases in uric acid in both serum and urine may be the result of not only changes in glomerular filtration but also proximal tubular function and secretion and synthesis by xanthine oxidase [1]. As seen in our study in preeclampsia a decrease in NO (vasodilatation) causes vasoconstriction (increase in BP) and increased excretion of uric acid in urine. Other studies have reported that women with preeclampsia and hyperuricemia have a more severe form of preeclampsia with an increased risk for preterm and small for gestational age births [20-22]. A study by Mazalli et al [23] demonstrated that inhibiting the activity of uricase in a rat model leads to the development of hypertension and renal injury; these changes were mediated by the stimulation of the renin angiotensin system and inhibition of nitric oxide synthase. Increase in urinary excretion of uric acid in preeclampsia is probably because of increased uric acid in capillary plasma entering the glomerulus and increased secretion into the lumen in the distal portion of proximal tubule.

5. Conclusion

In conclusion, we have observed that deficiency of NO and increase in serum uric acid levels are related to preeclampsia. Urine uric acid to creatinine ratio increased with the decrease in NO levels and can be used as a marker for preeclampsia. However, further studies on a larger population needs to be undertaken to validate its sensitivity and specificity.

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