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Research Article

Relation of Hyperuricemia with Maternal and Perinatal Complications in Severe Preeclampsia

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Abstract

Background: The relationship between hyperuricemia and hypertensive disorders is well established, however, until today the participation of uric acid in the clinical course of severe preeclampsia have not been elucidated. The measurement of uric acid is a test available to most hospitals, and its role in severe preeclampsia may have a high impact on patients with this disease.

Objective: To determine whether serum levels of uric acid are related to maternal and perinatal outcome in severe preeclampsia.

Material and methods: A prospective, cross-sectional comparative study was designed. A sample of 200 patients, 100 with severe preeclampsia and 100 with normotensive pregnancy was obtained. Uric acid was recorded as well as clinical variables, laboratory and fetal growth. Was taken as elevated uric acid the presence of more than 6.0 mg/dl. To relate the significance of uric acid levels with variables Chi square tests and Mann Whitney U test were applied. Was accepted as significant any p value less than 0.05.

Results: Significant difference (p = 0.05) was observed when comparing the levels of uric acid between the two groups. When comparing patients with healthy patients with severe preeclampsia and uric acid greater than 6 mg / dl significant differences in prematurity, Apgar score less than 6 points the minute of birth, admission to NICU, presence of respiratory distress syndrome, identified restriction intrauterine growth, higher systolic blood pressure of 160 mm/Hg, blood pressure greater than 90 mm/Hg; and the alteration of various laboratory values as platelets less than 100,000/mm3, GOT > 70 IU/l, GPT IU/L > 70, LD > 600 IU/L and urine proteins > 300 mg/dl.

Conclusions: Values greater than 6 mg / dl of serum uric acid in patients with severe preeclampsia is a useful and simple marker that can be associated with the presence of adverse fetal and maternal effects.

Keywords: *Severe preeclampsia; Uric acid*

Introduction

The association between hyperuricemia with preeclampsia is known since 1917 and the relationship between the degree of hyperuricemia and the severity of the preeclampsia was described in 1934 [1].

Since then there have been several studies on the role of uric acid in the preeclampsia, however, until our days the participation of uric acid in the pathophysiology and clinical evolution of preeclampsia has been controversial.

The relationship between uric acid and the development of arterial hypertension not related to pregnancy is perfectly established, so that in addition to being considered a biomarker of hypertension, it is also believed that has an important role to play in its etiology [2].

In the first trimester of pregnancy uric acid levels decrease generally to 3 mg/dl or less, as well as the increase in the glomerular filtrate. These levels increase in the second trimester and reach their highest level in the third trimester of gestation, reaching levels of 4 to 5 mg/dl [3].

The placenta, in normal pregnancy, is a source of purines, which also explains the physiologic increase the levels of uric acid [1].

The uric acid is the end product of purine catabolism by the enzymatic action of the xantine oxidor reductase (XOR). This enzyme has two forms that are convertible between them, the xantine oxidase (XO) and the xantine dehydrogenase (XDH) [4].

The XO reduces molecular oxygen, while the XDH reduces both oxygen and the NAD+ taking a great affinity for the second substrate. In addition, the XDH is more abundant in vivo and can be converted to XO in an irreversible manner by a variety of enzymes such as trypsin, chymotrypsin and pancreatin [4].

The liver and the small intestine are the major sources of XO, but currently there is evidence that both the heart and the vascular endothelium express XO. The main enzyme action of the XO is the catalytic conversion of consecutive hypoxanthine to xanthine and then from xanthine to uric acid. As byproducts of these reactions, are formed powerful EROs, molecules that possess high reactivity with other substrates, such as hydrogen peroxide (H_2O_2) and superoxide anion (O_2) [6]. The uric acid is mainly excreted by the kidneys and its plasma concentration depends on the pH of the urine, urine volume, body volume, renal function, diet and use of certain medications [4-6].

It is actually believed that the uric acid increases in the preeclampsia due to a combination of several factors such as the decrease of the glomerular filtration, the endothelial lesion and the proinflammatory state [5].

There is evidence that demonstrates the relationship of the uric acid in the endothelial dysfunction characteristic of the preeclampsia [1]. Some of the actions of the uric acid that contribute to the endothelial dysfunction during the preeclampsia are:

1. Potent inhibitor of the endothelial function [3].
2. Locks the role of VEGF [3].
3. Inhibits the trophoblastic invasion *in vitro* [3].
4. Stimulates the inflammatory response by stimulating the IL-1, IL-6 and TNF-alpha [5].

The presence of high levels of uric acid in the first trimester has been associated with 3.22 times increased risk of gestational hypertension and preeclampsia [2].

Base on the above, it has been postulated that the uric acid in the preeclamptic patient is not only a biomarker, but it contributes to the pathogenesis of the same [5].

Several studies have linked high levels of uric acid with the increased of fetal morbidity and mortality [6]. In women with pregnancy hypertensive disease uric acid levels correlate with the pulsatility index of the umbilical artery and the middle cerebral artery [6]. There is also a correlation between levels of uric acid and acid parameters fetal bases [5,6]. The fetuses exposed to hypoxia (a decrease of the placental perfusion) have elevated serum levels of metabolites of the purine [5,6].

High uric acid levels greater than 7.1 mg/dl predict a pH of the umbilical artery less than 7.15 (sensitivity 42%, specificity of 92%) [6].

The relationship between hyperuricemia and hypertensive disorders has been well established, however, until our days the participation of uric acid in the pathophysiology and clinical evolution of severe preeclampsia has not been clarified. The measurement of uric acid is a test within the reach of most of the hospital centers, so that to define its role in severe preeclampsia can have a high impact on the patients with this pathology.

Material and Methods

The objective of this study was to determine if the serum levels of uric acid are related with the maternal and perinatal result in severe preeclampsia, for which was designed a prospective, cross-sectional and comparative study. In the present study included randomly 200 patients attended in the department of obstetrics of the Obstetrics and Gynecology, Hospital "Dr. Luis Castelazo Ayala" IMSS and in the General Hospital of Mexico "Dr. Eduardo Liceaga" SSA, Mexico. Of the total of patients 100 had a diagnosis of severe preeclampsia and 100 were healthy patients with normal pregnancy. We excluded patients with pregnancy less of 20 weeks of gestation or with concomitant diseases. Whit the prior inform consent, to each patient there was realize the extraction of 5 mL of peripheral blood, for the measurement of uric acid. We took as increased uric acid the presence of more than 6.0 mg/dl. We defined adverse fetal results the presence of one or more of the following nominal variables:

1. Apgar score less than or equal to 6 at birth or at 5 minutes.
2. Acute Fetal Suffering.
3. Respiratory distress syndrome.

Of each group we described the general characteristics and the measures of central tendency (average, fashion and median), measures of dispersion (range and standard deviation), for their statistical analysis. To relate the significance of uric acid levels with the dependent variables we applied the tests of X2 and Mann Whitney U. It was accepted as significant any value of p less than 0.05. The statistical analysis was realized with the STATA program version 12.0 (Stata Corp, College Station, TX, USA).

Results

The general characteristics of the studied groups are described in Tables 1 and 2. The age and body mass index presents no significant difference between both groups.

Parameter	Healthy Pregnancy (n=100)	Severe Preeclampsia (n=100)	P*
Age	26.1 ± 6.4	27.1 ± 7.27	NS
BMI	28.5 ± 2.9	27.6 ± 3.9	NS

Table 1: *Demographic variables.*

BMI: Body mass index, SDG: weeks of gestation. ***Mann Whitney U**

Age Group	Healthy Pregnancy	Severe Preeclampsia
15 to 20 years	13 (13%)	13 (13%)
21 to 25 years	30 (30%)	19 (19%)
26 to 30 years	25 (25%)	29 (29%)
31 to 35 years	18 (18%)	20 (20%)
36 to 40 years	14 (14%)	19 (19%)
Total	**100 (100%)**	**100 (100%)**

Table 2: *Classification by age groups.*

The mean and standard deviation of the values of blood pressure (TA) systolic and diastolic in both groups are represented in table 3.

Parameter	Healthy Pregnancy (n=100)	Severe Preeclampsia (n=100)	P*
SBP	120 ± 09	148.92 ± 17	0.05
DBP	77.6 ± 9.21	93.37 ± 11.03	0.05

Table 3: *Clinical Variables.*

SBP: systolic blood pressure. DBP: diastolic blood pressure. ***Mann Whitney U**

When comparing the laboratory values between the two groups, we found significant differences between the values of uric acid (p=0.05), creatinine, Glutamic--oxaloacetic transaminase (GOT), Glutamic--pyruvic transaminase(GPT), Lactate dehydrogenase (LD), direct bilirubin (DB), platelets and hemoglobin (table 4).

Parameter	Healthy Pregnancy (n=100)	Severe Preeclampsia (n=100)	P*
Uric acid	3.99 ± 0.77	5.43 ± 1.38	0.05
Creatinine	0.64 ± 0.5	0.72 ± 0.22	0.05
GOT	18.6 ± 34	25.9 ± 129	0.05
GPT	31.5 ± 60.7	40.1 ± 108	0.05
LD	52.8 ± 55	205.52 ± 136.4	0.05
DB	0.09 ± 0.14	0.07 ± 0.143	0.01
IB	0.22 ± 0.14	0.22 ± 0.2	NS
TB	0.32 ± 0.18	0.32 ± 0.3	NS
Platelets	194.646 ± 73 530	155.700 ± 125.810	0.05
Hemoglobin	12.2 ± 1.7	11.97 ± 4.32	0.05
Leukocytes	8.8 ± 2.92	9.2 ± 22.3	NS

Table 4: *Laboratory values.*

GOT: **Glutamic-oxaloacetic transaminase.**GPT: **Glutamic-pyruvic transaminase.** LD: Lactate dehydrogenase. DB: direct bilirubin. IB: indirect bilirubin. TB: total bilirubin. ***Mann Whitney U**

Table 5 presents information concerning the perinatal variables and the comparison between both groups. Significant differences were observed in all the evaluated parameters: weeks of gestation at birth, birth weight, Apgar at one minute and at five minutes after birth.

Parameter	Healthy Pregnancy (n=100)	Severe Preeclampsia (n=100)	P*
Weeks at birth	38.2 ± 4.25	34.3 ± 7.4	0.05
Birth weight	2868.43 ± 501.7	1812 ± 974.9	0.039
Apgar at 1 minute	7.92 ± 0.43	6.02 ± 1.42	0.04
Apgar at 5 minutes	8.91 ± 0.25	0755 ± 1.68	0.05

Table 5: *Perinatal Parameters.*

With regard to completion of pregnancy, it should be noted that the birth of the 100% of the patients with severe preeclampsia was via cesarean section (table 6).

Parameter	Healthy Pregnancy (n=100)	Severe Preeclampsia (n=100)
Delivery	N=41 (41%)	N=0
Cesarean section	N=59 (59%)	N=100 (100%)

Table 6: *Termination of Pregnancy.*

The Patients with uric acid levels > 6 mg/dl between the groups of healthy patients and with severe preeclampsia is presented in table 7.

Healthy patients with UA < 6 mg/dl	Healthy patients with UA > 6 mg/dl	Patients with SP with UA < 6 mg/dl	Patients with SP with UA > 6 mg/dl
N=100 (100%)	N=0	N=58 (58%)	N=42 (42%)

UA: uric acid. SP: severe preeclampsia.

Table 7: *Patients with uric acid levels > 6 mg/dl between the groups of patients with severe preeclampsia and healthy patients.*

The distribution between patients with diagnosis of severe preeclampsia with increased uric acid and healthy patients, as well as its relationship with fetal, maternal clinical and laboratory variables is presented in table 8.

Variable	Healthy pregnancy with UA > 6 mg/dl (n)	Severe preeclampsia with UA> 6 mg/dl (n)	Value of p*
Fetal Variables			
Apgar at 1 minute < 6	1	12	0.05
Prematurity (<34 weeks)	4	17	0.05
Admission to intensive care unit	2	16	0.05
Death	0	1	NS
Intrauterine growth restriction	0	4	0.001
Respiratory distress syndrome	4	18	0.05
Maternal clinical variables			
SBP> 160 mm/Hg	1	18	0.05
DBP> 90 mm/Hg	4	23	0.05
Maternal bleeding > 500 ml	11	17	NS
Laboratory values			
Platelets <100 000 /mm^3	2	10	0.05
GOT> 70 IU/l	2	7	0.001
GPT> 70 IU/l	4	13	0.05

LD> 600 IU/l	0	3	0.006
Creatinine > 1.2 mg/dl	1	2	NS
Urine proteins> 300 mg/dl	0	8	0.05

Table 8: *Healthy and severe preeclampsia patients with uric acid >6 mg/dl.*

*Chi square, UA: uric acid, SBP: systolic blood pressure, DBP: diastolic blood pressure, GOT: **Glutamic—oxaloacetic transaminase,** GPT: **Glutamic--pyruvic transaminase,** LD: Lactate dehydrogenase.

The distribution between patients with diagnosis of severe preeclampsia with uric acid < 6 mg/dl and patients with severe preeclampsia and uric acid > 6 mg/dl, as well as its relationship with fetal, maternal clinical and laboratory variables is presented in table 9.

Variable	SP with UA< 6 mg/dl (n)	SP with UA> 6 mg/dl (n)	Value of p*
Fetal Variables			
Apgar at minute < 6	7	12	0.03
Prematurity (<34 SDG)	17	17	NS
Admission to intensive care unit	21	16	NS
Death	0	1	NS
Intrauterine growth restriction	2	4	NS
Respiratory distress syndrome	24	18	NS
Maternal clinical variables			
SBP> 160 mm/Hg	17	18	NS
DBP> 90 mm/Hg	42	23	NS
Maternal bleeding > 500 ml	5	17	
Laboratory values			
Platelets <100 000 /mm^3	5	10	0.03
GOT> 70 IU/l	8	7	NS
GPT> 70 IU/l	14	13	NS
LD> 600 IU/l	0	3	0.03
Creatinine > 1.2 mg/dl	0	2	0.03
Urine proteins> 300 mg/dl	1	8	NS

Table 9: *Patients with severe preeclampsia and values of uric acid.*

***Chi square.** UA: uric acid, SBP: systolic blood pressure, DBP: diastolic blood pressure, GOT: **Glutamic—oxaloacetic transaminase,** GPT: **Glutamic--pyruvic transaminase,** LD: Lactate dehydrogenase.

Discussion

In the present study we could demonstrate that there is a significant difference between the levels of uric acid in patients with severe preeclampsia in comparison with the group of healthy patients. In addition, we can affirm that, in comparison with the healthy patients, patients with severe preeclampsia and uric acid greater than 6 mg/dl presented significant differences in relation to various fetal complications as prematurity, Apgar score less than 6 points at one minute of birth, entrance to neonatal intensive care unit, presence of respiratory distress syndrome or intrauterine growth restriction; maternal complications such as presence of systolic blood pressure higher than 160 mm/Hg and blood pressure higher than 90 mm/Hg; as well as the alteration of various laboratory values such as platelet count lower than 100 000/mm3, GTO > 70 IU/l, GPT IU/l >70, LD>600 UI/l and urine proteins > 300 mg/dl. When comparing the levels of uric acid (taking as a point of court 6 mg/dl) in patients with severe preeclampsia, we found differences with respect to the Apgar score less than 6 points at one minute of birth, the platelet count lower than 100 000/mm3, creatinine > 1.2 mg/dl and DHL >600 IU/l.

For more than a hundred years the clinical utility of the uric acid has been widely discussed, several national and international studies have shown conflicting results, so that their role had been relegated in recent years, however, the present study and the growing current evidence on the role of uric acid in the pathophysiology of preeclampsia forces us to reevaluate the role of the same, not only as a prognostic marker, but also as part of the complex pathogenesis of preeclampsia to itself.

Taking into account our results we can say that the measurement of uric acid is a test which should be requested as a routine protocol study of the patients with severe preeclampsia.

Conclusion

It is on the basis of the results obtained in the present study conclude that the measurement of serum uric acid in patients with severe preeclampsia is a useful marker, simple and economic that can be associated with the presence of maternal and fetal adverse effects. The finding of a value of uric acid greater than 6 mg/dl in the patient with severe preeclampsia should alert on the possibility of complications that potentially put in risk the live or the function of the fetus or the mother, so that we have to act promptly and assertively.

In a highly technological age, where research and clinical approach of the preeclampsia leans on molecular studies and highly specialized measurements that represent high costs and therefore access to only a small portion of the affected population. It is essential not to lose the perspective of the usefulness and universally applicability of simple tests, such as the measurement of the uric acid in maternal serum. This concept takes on greater value in countries such as ours, where most of the maternal deaths of direct cause are due to complications arising from the late attention of preeclampsia. Many challenges remain in force regarding the prediction, prevention and treatment of patients with severe preeclampsia and their perinatal complications, however, this study gives a contribution in this regard.

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