ASSOCIATION OF SERUM URIC ACID AND C-REACTIVE PROTEIN LEVELS IN PREDICTION OF PRE-ECLAMPSIA

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Abstract

Background: Hypertensive disorders during pregnancy increase maternal and infant risk. The greatest impact is associated with the being pregnant-specific syndrome, preeclampsia, a always clinically worsening situation. PE is a complication of being pregnant, constituting a primary cause of maternal and foetal morbidity, and mortality Hyperuricemia and elevated CRP level, in pre-eclamptic patients need to be confirmed, in a designed method, wherein uric acid and CRP level are measured before the development of preeclampsia, or early in pregnancy, in order to identify and monitor the patients, "at risk of preeclampsia", and thus provide the best prenatal take care of these women and their babies.
Methods: The study become performed in Obstetrics and Gynecology department, PBM hospital, SPMC Medical College Bikaner, Rajasthan, India. The study duration was 12 months. It is a prospective type of study comprising of patients. Serum uric acid and C-reactive protein had been estimated along with different routine investigations for all patients attending. All the subjects have been divided into groups: (i) group-1 (study group): 60 diagnosed pre-eclamptic patients in 1/3 trimester of pregnancy (37-40 weeks) whose serum uric acid and CRP ranges were already raised during her antenatal visits in 2d trimester, (ii) group-2 (control group): 60 normal pregnant women of comparable gestational age
Results: The mean values of serum uric acid and CRP ranges remain higher in study group than that of control group. This difference is statistically significant (p= 0.02).
Conclusions: All the patients in study group whose measurement of uric acid and CRP levels were high, evolved pre-eclampsia. So, it can be fairly concluded, that the determined elevations in serum uric acid level or CRP level or both, preceded the development of pre-eclampsia.

Keywords: Pre-eclampsia, Serum uric acid levels, Serum CRP levels

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2. INTRODUCTION

Hypertensive disorders during pregnancy increase maternal and infant risk. The finest impact is associated with the pregnancy-specific syndrome, pre-eclampsia and a continually clinically worsening situation.

Preeclampsia (PE) develops in 4-5% of human pregnancies. It is characterized by an elevated blood pressure, more than 140/90 mm of Hg, on two separate occasions, taken 6 hours apart, within a period of one week, and evidence of proteinuria, which develops after 20 weeks of gestation. PE is a complication of pregnancy, constituting a major cause of maternal and foetal morbidity, and mortality. Several aetiologies have been implicated in the development of preeclampsia, including abnormal trophoblast invasion of uterine blood vessels and immunological intolerance between feto-placental and maternal tissues. Endothelial cellular dysfunction and inflammation are taken into consideration to have a role inside the pathophysiology of PE.

A generalized activation of circulating leukocytes, characteristic of inflammation, has been determined during PE. Furthermore, elevated concentrations of CRP and inflammatory cytokines have been reported in PE women. CRP is produced by the liver and the production is stimulated by using the inflammatory cytokines, interleukin-6 and TNF-alpha. CRP level increases during inflammatory response to tissue injury or infection. CRP, though now not pathology specific, because it will increase in a number of conditions, is an objective and sensitive index of overall inflammatory activity in the body.

Table 1: C-reactive protein (serum) - normal levels.

Units	Non pregnant adult	First Trimester	Second Trimester	Third Trimester
mg/L	0.2 – 4	2.39 -3.05	0.4 -20.3	0.4 – 8

Plasma CRP ranges upward push in cases of acute infection, malignancy & inflammatory diseases. It's been advised that increased ranges of CRP, in accordance with its proposed function, may also reflect the inflammatory response characteristics of preeclampsia. Raised serum uric acid (UA) is one of the characteristic findings in pre-eclampsia. In medical practice, serum UA determination is considered to be part of the work up, in women with preeclampsia, to monitor disease severity, and aid management, of these women.

Uric acid is a product of purine degradation, catalyzed by the enzyme xanthine dehydrogenase/xanthine oxidase (XDH/XO). XDH is converted to its oxidase form XO, with the aid of several stimuli, including ischemia.[1] Purine metabolism by XO, couples the production of uric acid, with the production of the free radical superoxide (O2-), and, is implicated as a contributor to oxidative stress.[1] XDH/XO is found in most tissues, but is concentrated in the liver and gut. Recently, a circulating population of XO has been identified that increases dramatically, following ischemic tissue damage.[2] Increased circulating uric acid accompanies similar insults.[3] It's far speculated that circulating XO can bind to endothelium and lead to local oxidative injury.[4]

Hyperuricemia is a common finding in pre-eclamptic pregnancies. The elevation of uric acid in pre-eclamptic women, often precedes high blood pressure and proteinuria, the medical manifestations, used to diagnose the disorder.[5] There are several potential origins, for uric acid in preeclampsia; abnormal renal function, elevated tissue breakdown, acidosis and increased activity of the enzyme xanthine

oxidase/dehydrogenase.[6] however, despite hyper-uricemia antedating other medical findings of preeclampsia, it has historically been ascribed to reflect impaired renal function. Reduced UA clearance, secondary to decreased glomerular filtration rate, elevated reabsorption, and reduced secretion, may be at theorigin of increased serum levels in women with preeclampsia. It's miles one of the most consistent and earliest detectable changes, in preeclampsia and has been cited as a better predictor, of fetal risk, than blood pressure.

Uric acid is able to unfavorable adult vasculature, and could have comparable results in the placentae of pre eclamptic women. The placental vasculature lacks autonomic innervation, relying entirely upon locally produced or circulating substances, for hemodynamic control. [7] The primary vasoactive compound responsible, for the maintenance of optimized placental perfusion, is endothelial derived NO. Uric acid decreases eNOS activity limiting NO availability, and up-regulates COX-2 expression, with elevated generation, of the effective vasoconstrictor thromboxane.[8] A similar vaso-constrictive impact of uric acid inside the placentae of women with preeclampsia would compromise placental perfusion, and will inhibit fetal growth.

Table 2: Uric acid (serum) - normal levels.

Units	Nonpregnant female	First Trimester	Second Trimester	Third Trimester
mg/dL	2.5 - 5.6	2 - 4.2	2.4 - 4.9	3.1 - 6
µmol/L	149 - 333	119- 250	143 - 292	184 - 375

Pre-eclampsia is a potentially dangerous situation during antenatal period that culminates in events increasing maternal and fetal morbidity and mortality. Many times, the situation defies the treatment as soon as it's miles fully developed. Early diagnosis or recognition of the onset of pre eclamptic changes can help reduce and manipulate the situation, limiting the undesirable results. For this purpose, detection of these parameters, abnormal levels in early stage of developing pre-eclampsia can certainly achieve the aim of safe motherhood and baby survival.

The present study was conducted to study the role of increased levels of Uric acid and C-reactive protein in patients with pre-eclampsia.

1. METHODS

A prospective study became done in Obstetrics and Gynecology department, PBM hospital, SPMC Medical College Bikaner, Rajasthan, India for 12 months.

Inclusion criteria:

1. All antenatal patients who have singleton pregnancy.

Exclusion criteria:

1. All antenatal patients who are known cases of chronic hypertension.
2. All antenatal patients who have renal or cardiac disorders.
3. All antenatal patients who have inflammatory conditions, respiratory tract infections.
4. All antenatal patients with multiple gestations.

All the cases and controls in the study were subjected to detailed history.

Systemic examination with special connection with oedema, blood pressure and gestational age was done routine Antenatal Investigations had been recorded in the proforma specially designed for the study. Serum uric acid ranges and CRP ranges were measured for all of the patients attending the OPD and had been followed up till delivery.

Those available data was co-related as according to further study design. The

prognosis of preeclampsia became based on the definition of American college of obstetrics and gynaecology

Table 3: Comparison of mean ± SD of blood pressure (mmHg) level between the study group and control group.

Parameter (mmHg)	No. of patients	Study Group		Control Group		t-test	P value
		Mean	SD	Mean	SD		
Systolic blood pressure	60	152.09	8.4	115.3	9.3	21.24	0.0001
Diastolic pressure	60	102.3	8.09	75.06	7.4	18.06	0.0001

The comparison of mean ± SD (mmHg) of blood pressure between the study groups and controls group. it is visible that the mean ± SD of systolic as well as diastolic blood pressure levels in pre-eclamptic women (152.09 ± 8.4 mmHg, 102.3 ± 8.09 mmHg) are much higher than that of normal pregnant women (115.3 ± 9.3 mmHg, 75.6 ± 7.4 mmHg).

I. Systolic blood pressure more than 140 mmHg or upward push of at least 30 mmHg.

II. Diastolic blood pressure greater than 90 mmHg or A upward push of as a minimum 15 mmHg (Measured on occasions at least 6 hours apart) and proteinuria of 300 Mg or more in 24 hours urine collection or protein concentration of 1 gm/L (on occasions of at least 6 hours apart), or ≥ 2+ in mild preeclampsia and >3+ in severe preeclampsia by dipstick method.

All the subjects were divided into two groups:

Group 1 (Study group):
60 Diagnosed pre-eclamptic patients in third trimester of pregnancy (37-40 weeks) whose serum uric acid and CRP ranges have been already raised at some point of her antenatal visits in 2nd trimester.

Group 2 (Control group):
60 Normal pregnant women of comparable gestational age.

Statistical methods:
Records can be analysed and appropriate statistical methods like chi-square test, population test or T-test, Pearson's formula may be employed to analyse data throughout study.

2. RESULTS

Table 4: CRP levels in study group and control group.

CRP (mg/L)	Study group no. (%)	Control group no. (%)	P value
0.4 - 8	25(49%)	45(88%)	0.0001
> 8	35(51%)	15(12%)	

CRP level is inside moderate increase range in 49 % patients of study group and 88% patients of control group. It is above the upper limit of normal range (i.e. >8 mg/L) in 51 % patients of study group and 12% patients of control group. The data is statistically significant (P=0.0001).

Table 5: Uric acid levels in study group and control group.

Uric acid (mg %)	Study group no. (%)	Control group no. (%)	P value
< 3	0	9(13%)	0.0001
3 to 6	34(61%)	48(85%)	
> 6	26(39%)	3(2%)	

It is observed that uric acid level is within slight increase range in 61% of study group (pre-eclamptic group) and 85 % patients of control group, whereas it is above the upper limit of normal range (i.e. >6 mg%) in 39 % of study group and 2 % patients in control group. The data is statistically significant (P=0.0001).

Table 6: Relationship /comparison between mean value of serum uric acid level and CRP level in study group and control group.

Parameters	Group	Mean ± SD	Median	p value
CRP	Study	6.8 ±3.4	8.4	0.02
	Control	5.4 ±2.8	5.4	
Uric acid	Study	5.8 ±1.8	5.4	0.0001
	Control	4.1 ±1.05	4.2	

It is determined that mean value of serum uric acid level in study group is 5.8+1.8 mg% which is quite higher than that of control group i.e. 4.1± 1.05 mg% and this difference is statistically significant (p =0.0001). On the other, the mean value of serum CRP level in study group is higher (6.8±3.4 mg/L) than that of control group (5.4±2.8 mg/L), this difference is statistically significant (p=0.02). The mean values of serum uric acid and CRP levels remain higher in study group than that of control group.

In control group, the rise in CRP ranges and Uric acid ranges stay less in comparison of the study group (table 6), and there was no upward push in blood strain. The mean values of serum uric acid and CRP ranges stay higher in study group than that of control group. There is a strong association of elevated ranges of uric acid and CRP, with level of increase in blood pressure.

Table 7: Mode of delivery.

Mode of delivery	Study group (n=60) No. (%)	Control group (n=60) No. (%)
Normal vaginal delivery	40(75%)	45 (85%)
LSCS	11(21%)	12(10 %)
Instrumental delivery (forceps)	9(4%)	3(5 %)

In study group, 40 (75%) cases had normal vaginal delivery. 11 (21%) had LSCS; 2 for foetal distress, 1 for thick meconium, 5 for thin meconium, 3 for cephalo- Pelvic Disproportion.

In control group, 45 (85%) cases had normal vaginal delivery. 12 (10%) had LSCS; 2 for thick meconium; 8 for foetal distress; 2 for cephalo-pelvic disproportion. Outlet forceps deliveries had been to cut down the duration of 2d stage, & there by reducing the time of exposure to
Detrimental situation, as cervix was fully dilated in those cases.
The mean birth weight became 2.3 Kg in study group and 2.5 Kg in control group. The incidence of birth weight < 2.5 Kg became seen in 40 (80%) and 30 (60%) in study group and control group respectively. The occurrence of low birth weight (< 2.5 Kg), the difference was statistically significant ($p < 0.05$).
In study group, 15 (20%) neonates of study group were admitted to neonatal intensive care unit for various morbidities like birth asphyxia, meconium aspiration, intrauterine growth retardation, transient tachypnoea of newborn. only 4 (4%) of control group were admitted to neonatal intensive care unit. The difference within groups was statistically significant (P <0.05).
There had been 5 early neonatal deaths in study group and 2 early neonatal death in control group. The difference in the neonatal deaths became statistically non-significant between two groups (P=0.30). In study group, 2 neonate who died, the mode of delivery was LSCS and 3 neonates who died, delivered vaginally. In control group, there was 2 neonatal death and the mode of delivery was LSCS.
The reasons of deaths were following:

In study group:
One neonate died due to meconium aspiration syndrome.
Two died because of IUGR with early onset of sepsis.
The mothers of these three neonates had severe pre-eclampsia with serum uric acid and CRP levels greater than the upper limit of normal range. (CRP >8 mg/L and uric acid >6 mg %).

In control group:
One neonatal death was due to meconium aspiration syndrome with severe birth asphyxia.
In study group, there are 25 patients whose CRP and uric acid levels have been above the higher limit of the normal range (CRP > 8 mg/L and uric acid >6 mg %) at around 30 to 34 weeks of gestation. Those patients had progressed to severe pre-eclampsia. Their blood pressure became controlled with hypertensive drugs; tablet Labetalol (100mg) B.D. and tablet Methyl Dopa (250mg) T.I.D.
After delivery of these 25 patients (mothers), 8 neonates were admitted to neonatal intensive care unit.
Three neonates had IUGR and had been admitted for 2 weeks, for adequate weight again and antibiotic therapy. However, of those neonates died due to early onset of sepsis and one changed into returned to mom after 2 weeks.
 Had moderate birth asphyxia, and had been kept on ventilator for 12 hours followed by oxygen administration for 12-24 hours with antibiotic therapy. Those neonates had been returned to mother inside 24-48 hours.
 Three neonates had meconium aspiration syndrome. They have been given gastric lavage and were on ventilator. One neonate died, within 12 hours of birth. The other were stepped right down to oxygen for next 24 hours together with antibiotic therapy. These neonates were returned to mom within 48-72 hours.
In rest of 34 patients, there were moderate increase CRP and uric acid levels (CRP -0.4 to 7.9 mg/L and uric acid –3 to 5.9 mg %) at around 30-34 weeks of gestations. These patients had developed mild pre-eclampsia. Their blood pressure become managed by way of a single anti-hypertensive drug; tablet Labetalol (100 mg) B.D
After delivery of these 34 patients (mothers), 3 neonates were admitted to neonatal intensive care unit

 Two neonates had meconium aspiration syndrome and became given gastric lavage and was kept on CPAP for 24 hours observed by means of oxygen by hood for next 12 hours along with antibiotic therapy. The neonate became returned to mother within 48 hours.

 The other one had IUGR and was admitted for 2 weeks, for adequate weight gain and antibiotic therapy. The neonate become returned to mother after weeks.

In control group, only 3 neonatal admissions were there in intensive care unit

 Two neonates for transient tachypnoea of newborn was administered oxygen for 12 hours and became returned to mother within 24 hours.

 The other neonate had meconium aspiration syndrome with birth asphyxia and become kept on ventilator but could not survive and died within 6 hours of birth. The patient (mother) had higher ranges of CRP and uric acid above the upper limit, however now not related to increased blood pressure. Also, the gestation age of the patient (mother) was 40 weeks, so meconium leakage became probably due to intrapartum placental dysfunction.

There was No maternal morbidity or mortality in our study.

3. DISCUSSION

The mean ± SD of blood pressure (mmHg) was extensively higher in preeclampsia (152.09 ± 8.4 mmHg, 102.3 ± 8.09 mmHg) compared with regular controls (systolic: 115.3 ± 9.3 mmHg, diastolic: 75.06 ± 7.4 mmHg). The level of serum uric acid was extensively higher in the study group than in the controls (5.8+1.8 mg/dl versus 4.1+1.05 mg/dl). In study group, 21% women have uric acid level more than upper limit of normal range (>6 mg%). The records is statistically very significant (P=zero.0001).

Increased serum uric acid ranges due to reduced renal urate excretion are frequently found in women with preeclampsia.[9] Soluble uric acid impairs nitric oxide generation in endothelial cells inducing endothelial dysfunction.[10] Besides the reduced clearance hyperuricemia in pre-eclampsia may be due to increased uric acid production due to trophoblast breakdown, cytokine release and ischemia. Uric acid can promote endothelial dysfunction, damage and inflammation, which leads to oxidation. So, preeclampsia, which is characterized by widespread endothelial dysfunction and inflammation, is probably propagated by means of uric acid.[11] It has additionally been reported that upward push in uric acid level in preeclampsia is secondary to placental damage leading to purine catabolism and production of uric acid.

The human placenta receives its blood supply from numerous uteroplacental arteries that are developed by the action of migratory interstitial and endovascular trophoblast into the walls of the spiral arterioles. This transforms the uteroplacental arterial bed into a low resistance, low-pressure, high-flow system. The conversion of the spiral arterioles of the non-pregnant uterus into the uteroplacental arteries has been termed physiologic changes.[12] In a normal pregnancy, these trophoblast-induced vascular changes extend all the way from the intervillous space to the starting place of the spiral arterioles from the radial arteries inside the inner one third of the myometrium. It is suggested that these vascular modifications are affected in stages: "the conversion of the decidual segments of the spiral arterioles with the aid of a wave of endovascular trophoblast migration within the first trimester and the myometrial segments by way of a subsequent wave within the 2nd trimester".[12]

This procedure is reportedly associated with massive fibrinoid formation and degeneration of the muscular layer within the arterial wall. Those vascular changes result in the conversion of about 100 to 150 spiral arterioles into distended, tortuous,

and funnel-shaped vessels that communicate thru multiple openings into the intervillous space. In contrast, pregnancies complicated by preeclampsia demonstrate insufficient maternal vascular response to placentation. In those pregnancies, the above-mentioned vascular changes are generally determined only in the decidual segments of the uteroplacental arteries. Hence, the myometrial segments of the spiral arterioles are left with their musculo-elastic structure, thereby leaving them attentive to hormonal influences.[12] Additionally, the number of properly-developed arterioles is smaller than that discovered in normotensive pregnancies. Kong and colleagues have postulated that this defective vascular reaction to placentation is because of inhibition of the second wave of endovascular trophoblast migration that normally takes place from about 16 weeks' gestation onward. These pathologic changes may additionally have the effect of curbing the elevated blood supply required by using the fetoplacental unit within the later stages of being pregnant, and correlate with reduced uteroplacental blood flow seen in maximum cases of preeclampsia. The hyperuricemia of preeclampsia has been variably suggested to be related to lactic acidosis, altered renal function, or oxidative stress. The currently favoured concept is that, elevated circulating uric acid is secondary to decreased renal urate clearance, as can be seen with hypovolemia. Uric acid is the cease product of purine catabolism catalysed through the enzyme xanthine oxidase/dehydrogenase. This bifunctional enzyme, in its dehydrogenase form, produces uric acid and reduced nicotinamide-adenine dinucleotide and, in the oxidase form, produces uric acid and superoxide. The enzyme is upregulated, and the expression of the oxidase form increased proportionally with hypoxia. Hence, elevated uric acid manufacturing occurs in a setting of hypoxia, local acidosis, or elevated tissue breakdown or with decreased renal function can increase oxidative stress - all of which might indicate more severe preeclampsia. Other than decreased renal clearance, there can also occurs elevated placental production of UA secondary to placental ischemia and increased trophoblast shedding, leading to similarly purine availability for breakdown. Foetuses exposed to hypoxia (e.g., secondary to decreased placental perfusion) are determined to have elevated serum levels of purine metabolites.[13] In preeclampsia, therefore, it is workable that those metabolites can cross into the maternal circulation to be degraded by means of maternal xanthine oxidase. These latter mechanisms may explain the relationship between raised UA levels and foetal growth retardation. However, the increase in UA ranges is just too large to be attributed entirely to the reduction of glomerular filtration rate; and so, there should also be decreased secretion or elevated reabsorption. In keeping with those considerations, UA can be an early marker of preeclampsia. in this study, the level of serum CRP was higher in pre-eclamptic patients than the normal pregnant women (6.8+ 3.4 mg/L versus 5.4 + 2.8 mg/L) and is significant (P=0.02).

The suggest values of serum CRP levels stay higher in study group than that of control group. A widespread positive correlation is observed between serum uric acid and serum CRP. In preeclampsia the level of CRP is increased. Native CRP is synthesized in a soluble form through hepatocytes and then secreted into the circulation. The production of CRP is caused via pro-inflammatory cytokines IL-1, IL-6 and IL-17 inside the liver, although extra hepatic production additionally makes contributions to systemic concentrations. Cytokines exert their biological effects on CRP, by signalling via their receptors on hepatic cells and activating different kinases and phosphatases, leading to the translocation of numerous transcription elements, on the CRP gene promoter, and

the production of CRP.[14] the only determinant of the plasma attention, is the rate of synthesis. The upward push in blood CRP after tissue insult, or injury is rapid and robust. In preeclampsia, when there's endothelial cell injury, or endothelial cell dysfunction, the concentration doubles every 8 hours, and peaks at 36-50 hours, even though that depends at the stimulus and its severity. In response to an inflammatory insult, CRP concentration can increase above 500 mg/l and these quantities to as a good deal as a 1000-fold or extra awareness alternate.[15,16] But in case of preeclampsia, observed by superimposed infection, level of CRP increment is acutely higher. there may be now, clear appreciation for the role of cell adhesion molecules, angiogenic proteins, and activation of the inflammatory system in the pathogenesis of microvascular disorder in patients with preeclampsia.[17] This gives a clear proof for an exaggerated inflammatory response (abnormal cytokine production and neutrophil activation) in women with the clinical findings of preeclampsia.[18,19]

In study group, there are 26 patients, whose CRP and uric acid ranges were above the upper limit of the normal range (CRP >8 mg/L and uric acid >6 mg %) at around 30 to 34 weeks of gestation. Those patients had improved to severe pre-eclampsia and anti-hypertensive drugs, for manage of blood pressure had been given. With early prediction, there's reduced possibility of severity of pre-eclampsia. This led to reduced perinatal morbidity to 33%, which could have been otherwise higher, had the treatment started much later.

Of these 34 patients, increase in CRP and uric acid level become in midrange, which raised the possibility of mild severity of pre-eclampsia. Hence, handled with single hypertensive drug for control of blood pressure. Only 2 neonates, required admission in neonatal intensive care unit with a limited morbidity. One neonate had whole recovery within 48 hours. Some other one, required prolonged care, due to restrained growth. Otherwise, relaxation of the patients had good perinatal outcome.

4. CONCLUSIONS

All the patients in study group whose measurement of uric acid and CRP levels were high, evolved pre-eclampsia. So, it can be fairly concluded, that the determined elevations in serum uric acid level or CRP level or both, preceded the development of pre-eclampsia.

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