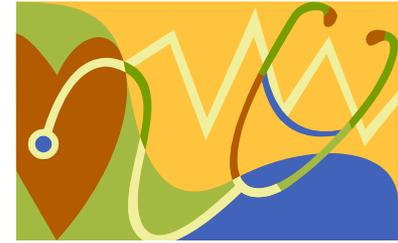




URIC ACID AS A BIOMARKER FOR PREECLAMPSIA

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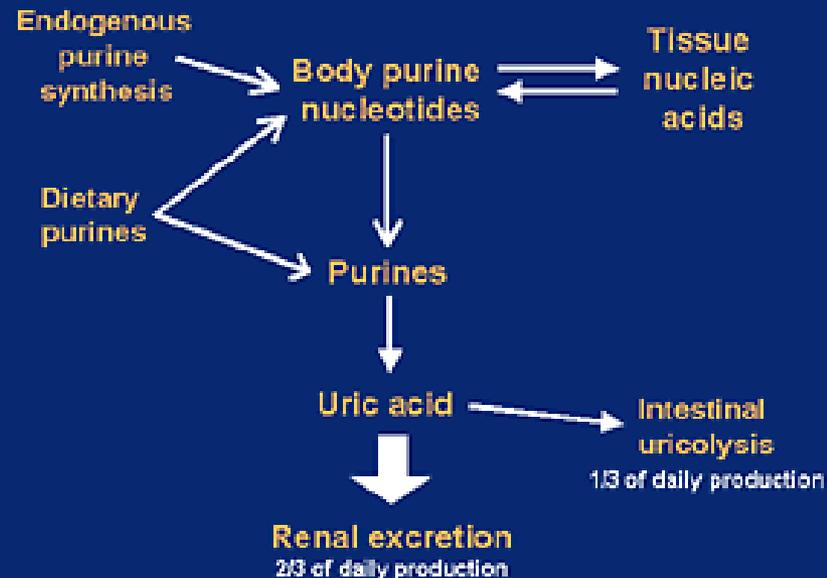
HYPOTHESIS



- ▶ In 1917 Slemons and Bogert first determined that the maternal serum concentration of uric acid is elevated in Preeclampsia and Eclampsia, complications which can result in severe morbidity and even mortality in pregnant females¹
- ▶ Preeclampsia increases the risk of fetal death five-fold and kills fifty thousand women a year.
- ▶ We wanted to confirm that maternal serum uric acid level during pregnancy can be used as a biomarker for Preeclampsia and that the serum uric acid levels correspond to the severity of Preeclampsia.

INTRODUCTION

Schematic Overview of the Production and Elimination of Uric Acid



Koopman, ed. In: *Arthritis and Allied Conditions*. 14th ed. Lippincott, Williams and Wilkins; 2001:2283.

URIC ACID PRODUCTION AND ELMINATION



- ▶ Uric acid is a product of purine metabolism. Most of the purines are synthesized in the liver but some come directly from food.
- ▶ $2/3^{\text{rd}}$ of the uric acid is excreted in the kidneys and the remainder via the GI tract.
- ▶ In the kidneys uric acid undergoes both reabsorption and secretion but there is net reabsorption in the renal tubules (88%-93% of the filtered load)

URIC ACID LEVELS IN NORMAL PREGNANCY



- ▶ In normal pregnancy the serum uric acid concentration is 25-35% lower than non-pregnant levels during most of the pregnancy.
- ▶ Toward the end of pregnancy the level rise towards normal.
- ▶ The mechanism involved is increased glomerular filtration during pregnancy and decreased fractional reabsorption of uric acid in the proximal renal tubules during pregnancy.

URIC ACID LEVELS IN PREECLAMPSIA



- ▶ Defective second stage of trophoblastic invasion in the placenta and production of an ischemic metabolite.
- ▶ That ischemic metabolite causes peripheral vasoconstriction in Systemic vessels, glomeruli, liver, CNS, eyes.
- ▶ Glomerular vasoconstriction and capillary bed damage (Glomerular Endotheliosis).
- ▶ Reduced GFR and increased Proximal tubular uric acid net reabsorption leading to raised serum levels.

Other reasons of elevated uric acid levels in Preeclampsia

- ▶ Other less significant mechanisms of increased uric acid tubular reabsorption are increased sympathetic activity, suppressed angiotensin system activity and reduced estrogen level² .
- ▶ Some have argued that raised serum lactate levels in Preeclampsia also decreases the tubular secretion of uric acid.^{3,4}
- ▶ Studies have used probenid which reduces tubular reabsorption and normalizes serum uric acid in preeclampsia patients showing that increased tubular reabsorption is the predominant mechanism of elevated uric acid level in Preeclampsia.^{5,6}

Continued...

- ▶ Latest studies show that uric acid may itself have a pathogenic role in Preeclampsia resulting in a vicious cycle of disease.



Why we did this study...



- ▶ Knowing that serum uric acid level is elevated in Preeclampsia we measured uric acid levels in pregnant women with and without pregnancy associated hypertension.
- ▶ To revisit uric acid as a useful biomarker of this deadly disease.
- ▶ A biomarker which is extremely cheap and widely available.
- ▶ A biomarker which has the potential to save the precious lives of the mother and fetus.
- ▶ Studies with newer biomarkers have shown variable and inconsistent results.

RESEARCH DESIGN AND METHODS

- ▶ Design: Retrospective Case Control Study.
- ▶ Study Endpoint: Preeclampsia/ Toxemia of Pregnancy.



STUDY GROUP



- ▶ 101 patients with established diagnosis of Preeclampsia fulfilling our criteria;
 1. Gestational Age \geq 20 weeks
 2. Peak Blood pressure: 140/90 mmHg
 3. Proteinuria \geq 0.3 grams/day

- ▶ Obtained from hospital registry (2004-2013).

- ▶ Their demographical information, vitals and lab work obtained from Soarian Database (EMR).

CONTROL GROUP

- ▶ All nulliparous and multiparous women with uneventful normal pregnancies and healthy babies.
 - ▶ We had to generate our own control group since uric acid levels were not routinely checked for normal low risk pregnancies.
 - ▶ After IRB approval and with the consent of the patients we started adding serum uric acid level as part of normal prenatal blood work for women coming in our outpatient clinic in their third trimesters.
 - ▶ These women were then followed till delivery.
 - ▶ Our control was comprised of 61 women with uncomplicated pregnancies.
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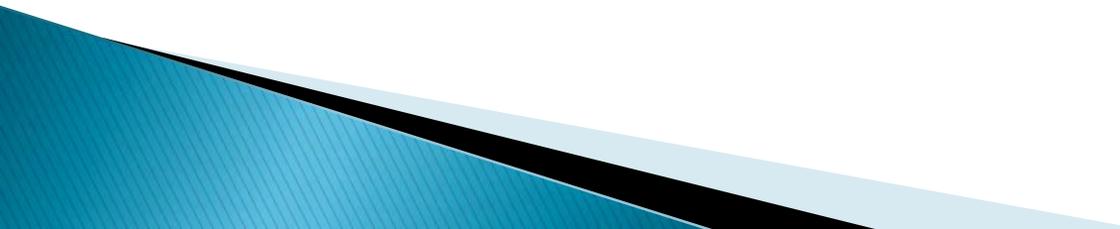
COMPARISON



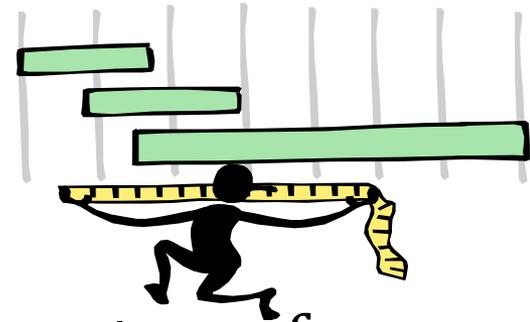
CHARACTERISTICS	STUDY GROUP	CONTROL GROUP
Number of women	101	61
Peak blood Pressure (mmHg)	>140/90	<140/90
Proteinuria (grms/day)	≥0.3	None
Gestational Age (weeks)	≥20	≥20

EXCLUSION CRITERIA

Women with chronic medical conditions such as:

1. Hyper uricemia.
 2. Renal dysfunction.
 3. Liver Dysfunction.
 4. Chronic Hypertension.
 5. Gout.
 6. History of Drug and alcohol abuse.
- 

MEASUREMENTS



- Serum uric acid levels during third trimesters of pregnancy were noted for study group and control group
- Sensitivity and Specificity of uric acid as a biomarker of Preeclampsia was calculated.
- Positive and negative predictive values of uric acid as a biomarker were also calculated.

MEASUREMENTS....

- ▶ Standard deviation and 95% Confidence intervals and mean serum uric acid levels in complicated pregnancies and uncomplicated pregnancies were calculated.
 - ▶ P-value was determined to assess statistical significance of the uric acid level difference between the two groups.
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SUBGROUP ANALYSIS

- ▶ In the study group we also carried out a subgroup analysis comparing the uric acid level with severity of Preeclampsia.

- ▶ We trended serum uric acid level with:
 1. Peak systolic blood pressure.
 2. LFTs (AST and ALT)
 3. Proteinuria
 4. BUN/ Creatinine.

- ▶ Scatter Graphs depicting relationship between uric acid levels, peak systolic, diastolic blood pressures, proteinuria, AST and ALT were plotted.

- ▶ The correlation coefficients and the p values for each correlation were calculated.

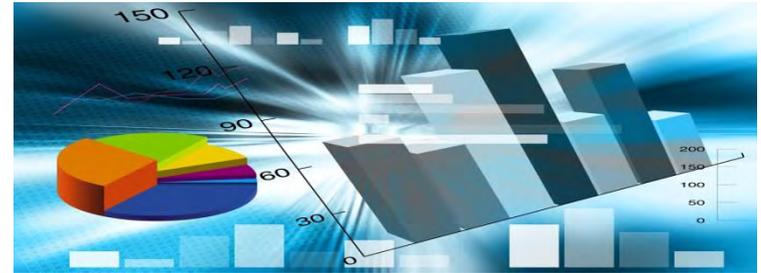
LOCATION OF STUDY

- ▶ Sisters of Charity Hospital and CHS Women's Health Center.
 - ▶ Data obtained from Soarian (EMR)
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PRIVACY

- ▶ Data was recorded with no specific patient identifiers.
- ▶ Serum uric acid levels were checked as part of normal prenatal blood work.

RESULTS



THIRD TRIMESTER SERUM URIC ACID	Preeclampsia	Number	Mean	Std. Deviation	Std. Error Mean
	No	61	3.264	1.4122	0.1808
	Yes	101	5.200	2.7081	0.2695

$t = -5.966$

$p = < 0.0001$

Confidence Interval = (-2.577, -1.2951)

URIC ACID/ PREECLAMPSIA MATRIX

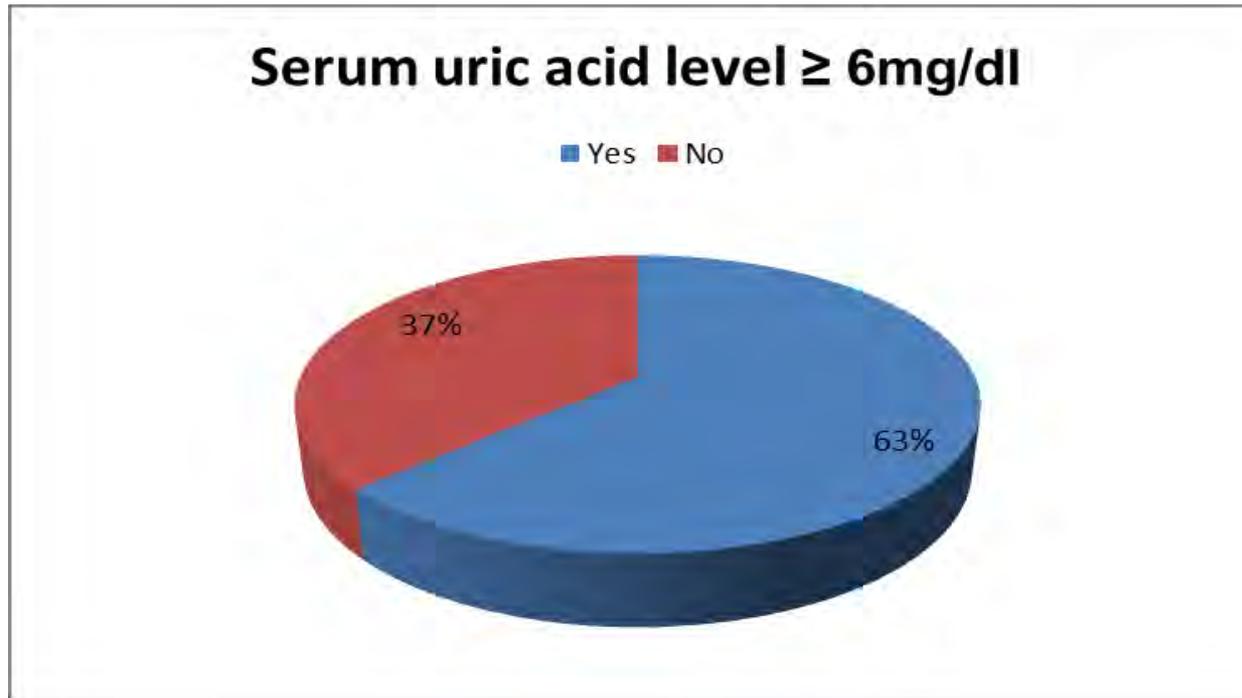
		Preeclampsia		Total
		Yes	No	
Uric Acid ≥6 mg/dl	Yes	64	4	68
	No	37	57	94
Total		101	61	162

SERUM URIC ACID AS A BIOMARKER

Sensitivity:	63%
Specificity:	93%
Positive Predictive Value:	94%
Negative Predictive Value:	61%

Study group

- 63% of patients in the study (Preeclampsia group) had uric acid level above 6mg/dl

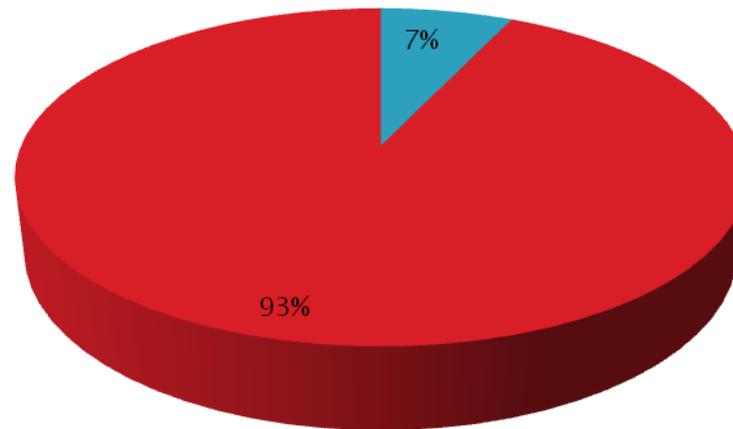


Control Group

Only 7 % of patients in the control group had uric acid level above 6 mg/dl

Uric acid > 6mg/dl

■ YES ■ NO



Meaning....

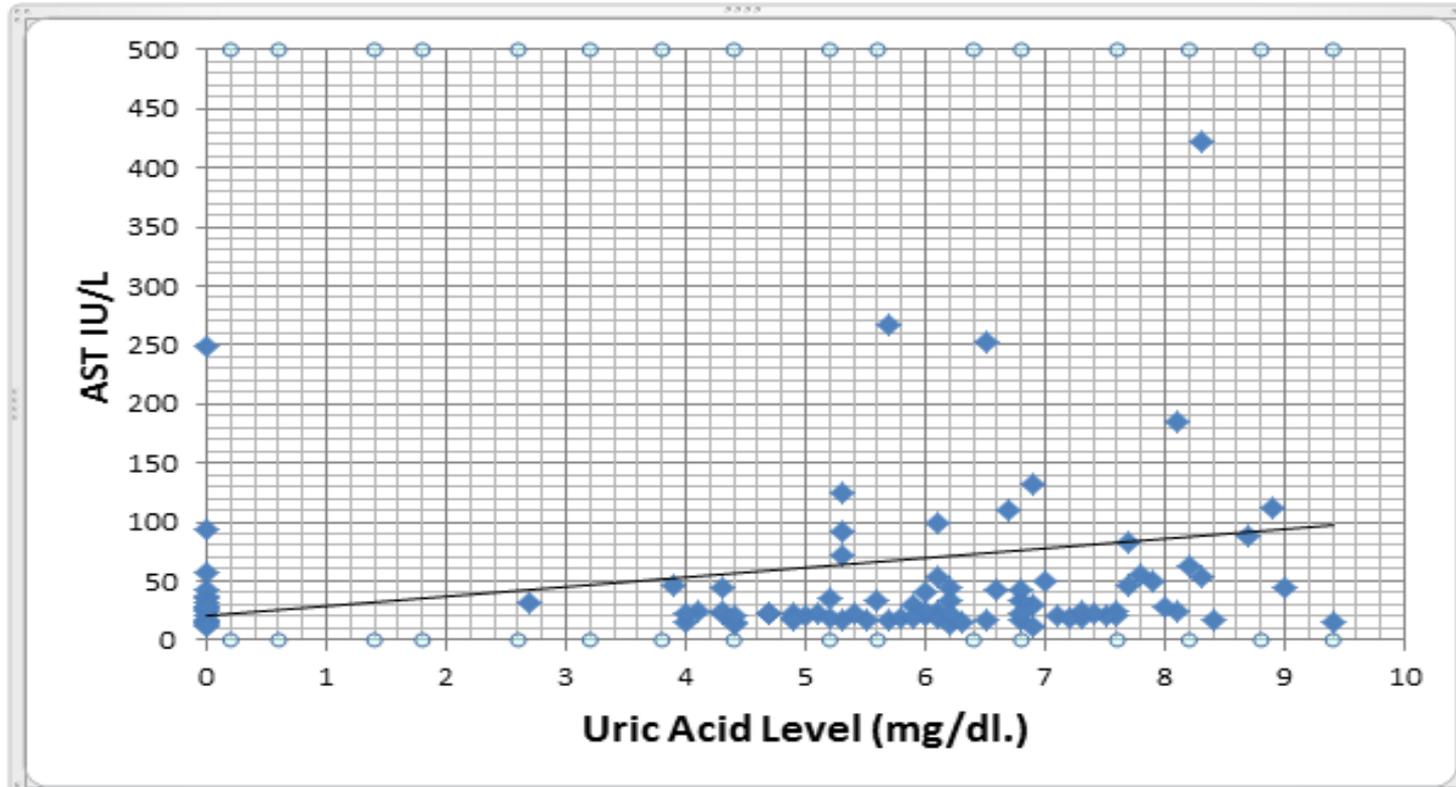
- ▶ If uric acid level more than 6 mg/dl in the third trimester chance of developing Preeclampsia 94%.
 - ▶ Positive predictive value= Believability of positive result=94%
 - ▶ Specificity also very high.
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SUBGROUP ANALYSIS

- ▶ Subgroup analysis in Preeclampsia group showing relationship between third trimester uric acid levels and severity of Preeclampsia as represented by;
 1. Peak systolic BP
 2. Derangement in AST, ALT
 3. Proteinuria.
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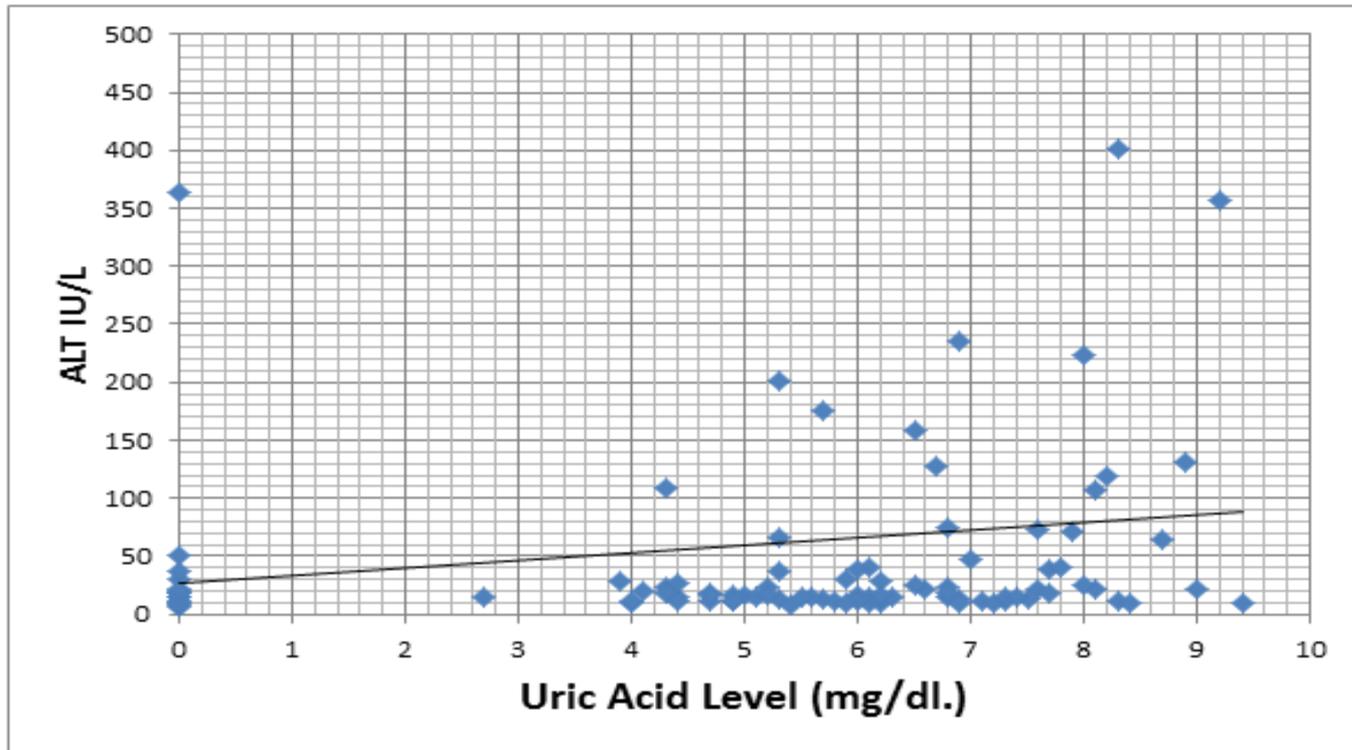
Uric acid level and AST

$\rho = .204$, ($p = .049$)



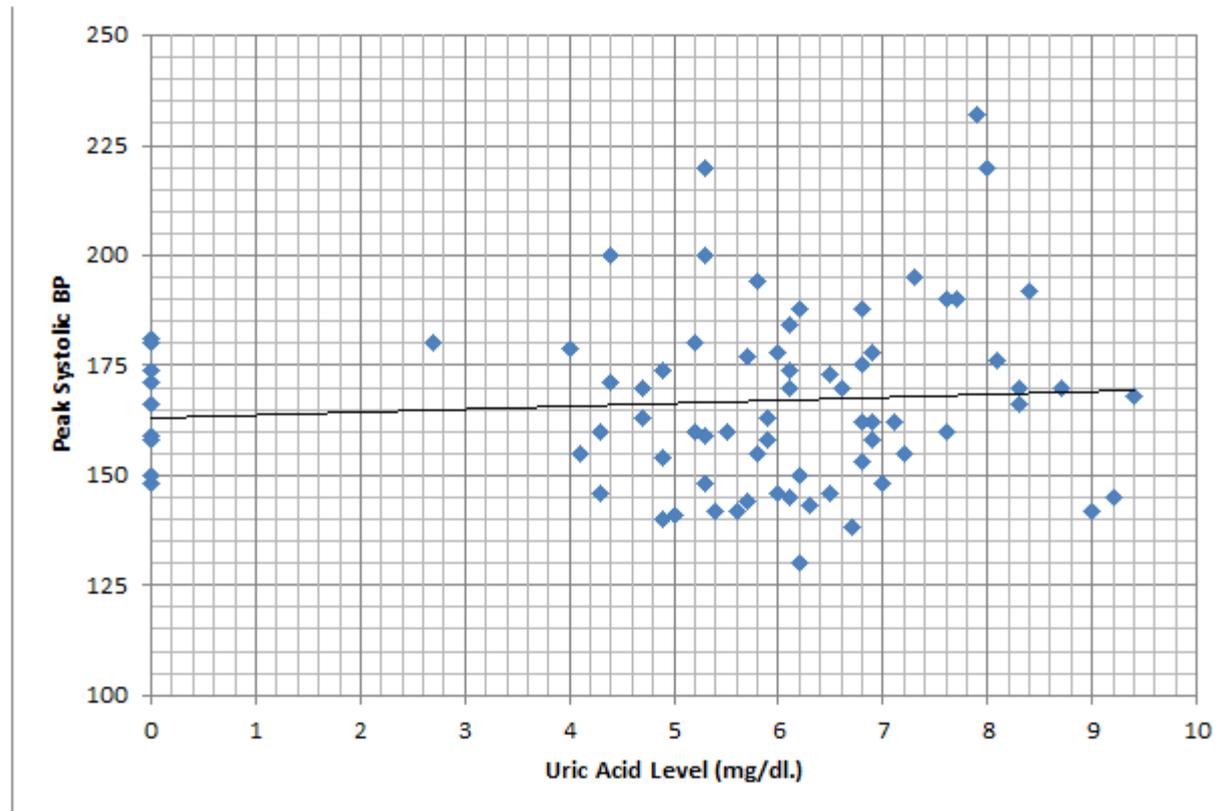
Uric acid level and ALT

$\rho = .208$, $p = .038$



Uric acid level and Peak systolic blood pressure

$\rho = .229, p = .003$



CONCLUSIONS



- ▶ Our study showed significant association between elevated maternal serum uric acid levels and Preeclampsia.
- ▶ Serum uric acid levels had positive correlation with severity of Preeclampsia. Thus serum uric acid level may be used to monitor the acute disease activity and possibly response to therapy.

CONCLUSIONS ...

- ▶ Compared to other biomarkers of Preeclampsia under study such as FLT-1 (fms related tyrosine kinase-1), PlGF (Placental growth factor), sENG (soluble Endoglin), urine Podocytes and Placental protein-3; uric acid is much cheaper, widely available and has much better sensitivity and specificity.
- ▶ The mean age of women with Preeclampsia was greater than mean age of females in normal pregnancies. This supports the theory that age may be an independent risk factor for developing Preeclampsia.

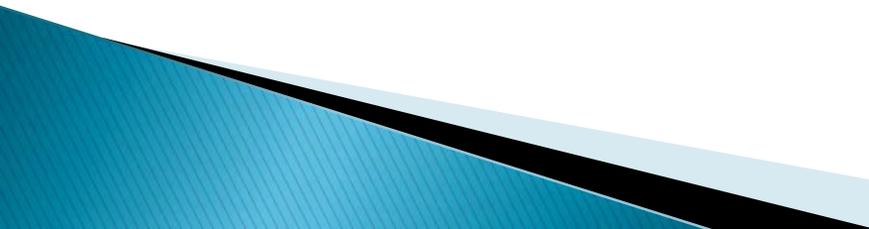
BIOMARKER COMPARISON

BIOMARKER	STUDY TYPE	SENSITIVITY	SPECIF	CONCLUSIONS
URIC ACID Serum/plasma	RETRO- CASE CONTROL	64%-84%	93%-98%	Cheap test. Reasonably sensitive and specific. Widely available.
sFLT1 serum/plasma	Nested case control; prospective; meta- analysis	26%-73.1%	88.5%- 100%	Sensitivity and specificity Varies according to the Timing of test and <u>population</u> ; maybe
sENG serum/plasma	Nested case control; prospective; meta- analysis	18%-85%	69%- 84.6%	useful in differentiating between CKD and chronic hypertension.
Placental growth factor (PlGF) Serum/urine	Nested case control; prospective; meta- analysis	32%-92.3%	51%-91%	

BIOMARKER COMPARISON...

BIOMARKER	STUDY TYPE	SENSITIVITY	SPECIF	CONCLUSIONS
sFLT1: PIGF, ratio	Nested case control; prospective;	62%-88.5%	51%-88.5%	Results vary by timing and population
PODOCYTUREA	Cross-sectional	38%-100%	70%-100%	Results no reproduced; may be elevated in high risk and normal pregnant females
PLACENTAL PROTEIN 3 Serum/plasma	Prospective	79%-100%	80-90%	Results mixed especially with <u>different methadologies</u> and assays.
UTERINE ARTERY DOPPLER VELOCIMETRY	prospective; meta-analysis			Results mixed

LIMITATIONS

- ▶ The maternal serum uric acid levels for the first and second trimester of pregnancy for the study and control groups were not available. Therefore we were not able to trend these levels from the beginning of pregnancy. So its not clear whether the uric acid levels were elevated during the acute disease phase or whether they were gradually trending up from the beginning of pregnancy.
 - ▶ Due to limited data we were not able to correlate uric acid levels with neurologic and ophthalmologic complications of preeclampsia.
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FUTURE DIRECTION

- ▶ We are planning a prospective study trending maternal serum uric acid levels from the beginning of pregnancy.

REFERENCES

- ▶ Slemmons J, Bogert L, The uric acid content of maternal fetal blood. *J Biol chem.*1917;32:63–69.
- ▶ Sica D, Schoolwerth A. Renal handling of organic anions and cations and renal excretion of uric acid. In: Brenner BM, eds. *The Kidney* 5th ed. Philadelphia: WB Saunders Company: 1996:607–626.
- ▶ Handler JS, The role of lactic acid in the reduced excretion of uric acid in toxemia of pregnancy. *J clin Invest* 1960;39:1526–1532.
- ▶ Fadel HE, Sabar MS, Mahran M, Seif el-din D, el Mahallawi MN. Serum uric acid in Preeclampsia and eclampsia. *J Egypt Med Assoc*, 1969; 52:12–23.
- ▶ Chesley LC, Williams LO. Renal glomerular and tubular function in relation to the hyperuricemia of preeclampsia and eclampsia. *Am J Obstet Gynecology* 1945; 50: 367–375.
- ▶ Martin AC, Brown MA. Could uric acid have a pathogenic role in pre-eclampsia. *Nat Rev Nephrol.* 2010 Dec;6(12):744–8. doi: 10.1038/nrneph.2010.125. Epub 2010 Oct 19.
- ▶ Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, et al. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. *BJOG.* 2012;119 (7):778–787.

THANK YOU

