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REVIEW ARTICLE

Uric Acid as an Additional Biomarker for Preeclampsia Beyond Renal Dysfunction

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ABSTRACT

Preeclampsia (PE) is a kind of pregnancy-associated hypertensive disorder that affects different organ systems during pregnancy and contributes as one of the important factors in contributing to both maternal and perinatal morbidity and mortality. On the other hand,"it" can lead to stroke, acute renal failure, HELLP syndrome, placental abruption, intrauterine fetal growth restriction, intrauterine fetal demise (IUFD), etc. PE occurs in 8-10% of all pregnancies in India. Earlier, the lack of advanced diagnostic approaches leads to its poor prediction at an early stage. During the past decade, there have been several studies in the diagnosis of PE by establishing simple, cheap, and cost-effective tools for diagnosis and prediction. Study of the blood uric acid levels in preeclampsia patients is quite prevalent, and considerable research in the same respect has been done in recent years. Nevertheless, experts suppose that high levels of uric acid in the blood are just a sign of a low kidney cleansing ability. In this regard, the authors of the article declare that they will present evidence showing that high levels of uric acid in preeclamptic patients can have sources other than the impairment of kidney function, with the activities of the placental ischemia-associated xanthine oxidase activity, the disruption of the trophoblast cell activity, and the activities of the NLRP3 inflammasome among such sources. Literature was identified through PubMed, Scopus, Embase, Google Scholar, and the WHO Global Health Library, guided by PRISMA principles adapted for narrative synthesis. Evidence from a large meta-analysis (196 studies, n ~ 39,540) indicates that serum UA is, on average, higher in PE than in normotensive pregnancy across gestation, with the difference increasing with advancing gestational age. Findings from several Indian clinical cohorts and international studies from Italy, China, Vietnam, and Colombia are summarized alongside comparative evidence for the established angiogenic markers sFlt-1 and PlGF. Reported diagnostic performance of UA is heterogeneous, with sensitivity generally in the range of 64–88% and specificity in the range of 48–93% depending on the population, cut-off, and gestational timing, indicating that UA functions best as a complementary rather than a standalone biomarker. This review discusses these findings cautiously, highlights conflicting and limiting evidence, and considers the potential role of point-of-care UA testing as an adjunct triage tool pending further prospective validation.

Keywords: Preeclampsia; serum uric acid; angiogenic biomarkers; maternal health; early diagnosis; healthcare technology; biomedical engineering.

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INTRODUCTION

Pre-eclampsia(PE) is thus an event that can either be urgent from the point of view of practice and a life-and-death issue which is crucially preventable. While there have been estimations of 5-10% of all pregnancies experiencing PE worldwide, the PE condition is still one of the most significant causes of maternal and perinatal deaths.[1] In health systems across India, pregnant women regularly present at PHCs with high blood pressure that signals possible nascent PE, but it will within days become a cause of potentially lethal maternal complications. Far more frequent than the occurrence of PE, then, is the shortage of appropriate diagnostic infrastructure – especially in rural settings. PE is defined as new-onset hypertension (systolic B P 140 mm/Hg or diastolic B P 90

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mm-Hg) recorded on two separate occasions at least 4 hours apart following 20 weeks of gestation, together with significant proteinuria (≥ 300mg/24h Urine) and/or evidence of maternal end-organ dysfunction.[1, 2] Notwithstanding the seemingly clear-cut definition, PE is a clinically heterogeneous syndrome that is likely to develop severe manifestations-seizures, stroke, hepatic haemorrhage, or placental abruption in very quick time, and even when the patient appears well. Prevalence estimates of PE globally have varied between 5-10% of pregnancies, and it has remained one of the primary causes of death of the mother and child.[1] In India, PE incidence varies from 8-10%; overall hypertensive disorders of pregnancy contribute to approx. 21% of maternal deaths; the burden is particularly disproportionately greater in peripheral/rural areas that represent most of the Indian population.[26] These lack essential laboratory facilities and adequate obstetric expertise, and referral is often so delayed that PE is recognized only after severe complications have developed. Elevated serum uric acid (UA) levels in patients with PE have been recognized for nearly a century, but it has conventionally been considered as the best biochemical marker for reduction in renal blood flow / glomerular filtration rate (GFR) rather than having a direct independent pathophysiological significance.

This review examines the evidence, mechanistic, epidemiologic, and pharmacological- indicating that the elevations of uric acid in PE might result, in part, through non-renal mechanisms that don't entirely involve a drop in GFR. This review suggests that UA elevation is not only a consequence but that it is in part causal, even though in pregnant women renal uric acid excretion increases, which leads to a reduction in serum urate levels. In this review, three key issues are discussed, Whether increased UA in PE might be in part explained by mechanisms such as placental ischaemia, xanthine oxidase activation and NLRP3 inflammasome associated activation, independent of the fall in the GFR, Whether elevated serum uric acid level might have some diagnostic value and prognostic value in different populations and in various gestational stages, along with other clinical and laboratory parameters, and clinical evidence from studies involving > 42,000 patients internationally, including several Indian cohorts.

MATERIALS AND METHODS

Databases searched and accessed via PubMed, Scopus, Embase, Google Scholar, WHO Global Health Library. Due to the differences in study methodology, a narrative search method was assumed to be the most suitable approach, rather than a wholly systematic search. The review considered selected PRISMA reporting principles. The quality and transparency of this narrative review were self-evaluated in relation to the Scale for the Assessment of Narrative Review Articles (SANRA).[32] and the self-assessment is reported in Table 3. The search strategy keywords derived from research areas on uric acid, preeclampsia, gestational hypertension, xanthine oxidase, NLRP3, inflammasomes, sFlt-1, PlGF, diagnostic accuracy, and maternal health linked with Boolean terms "AND" and "OR". There was no temporal limit on the search when dealing with the mechanistic and pathophysiologic data, but the search of studies focusing on diagnostic and clinical accuracy was limited to studies from 2005 onwards to be consistent with the contemporary diagnostic criteria (ACOG 2013 and ISSHP 2018) of preeclampsia.

The definition of pre-eclampsia used was that of ACOG 2013 or ISSHP 2018 definitions blood pressure 140/90 mmHg, with proteinuria >300 mg/24 hr, or any new-onset of multi-system signs, and that pre-eclampsia must have been diagnosed at ≥20 weeks gestation. The study include patients who were diagnosed with PE, serum or salivary UA was measured with a valid assay methodology (colorimetric or electrochemical based). Only those studies in which the UA measurement took place post delivery, and participants had a prior history of gout, renal failure, or post-renal transplantation were excluded, as they could independently raise UA concentrations, which would impact data interpretation. The identified records will be selected by title and abstract search before the full text document assessment against the eligibility criteria. Any article, where no control group, unclear diagnostic criteria for PE, or UA levels were considered when there was impaired renal function would be excluded. Method of UA detection and the value of any cut off points the rationale for exclusions the relevant results/findings including the number of PE patients in the study, the accuracy outcomes of the test as follows, sensitivity, specificity, the odds ratio.[9] or area under the ROC curve, as appropriate and corresponding findings are provided in Table 1.

SANRA-Based Quality Self-Assessment

A qualitative assessment of the methodology has been completed based on the Scale for the Assessment of Narrative Review Articles (SANRA).[32] a validated six item measure specifically designed for evaluating non-systematic reviews. SANRA based self-assessment is provided in Table 1 and gives the reader a readily reviewable guide as to how the review responds to each SANRA item and gives a methodological account instead of a PRISMA flow diagram, as the latter would fail to appropriately illustrate the process by which the original evidence has been located.

RESULTS AND DISCUSSION

Renal physiology in pregnancy and its influence on UA Interpretation

The interpretation of serum UA during pregnancy necessitates an appreciation of the physiology of normal pregnancy that is often omitted or trivialized in reviews of UA and PE. In healthy gestation, the increase in GFR by ~ 40–50% during the 1st trimester, secondary to the increase in plasma volume and renal vasodilation, increases urate clearance, and may actually lower serum UA to values that are less than nonpregnant levels during early gestation.[1,2] With advancing pregnancy, particularly during the 3rd trimester, changes in GFR dependent urate clearance and increased re-absorption of urate in the tubules elevate the serum UA even in healthy

Table 1. Self-assessment of this narrative review against the six SANRA criteria.[32]

Item	*SANRA Criterion*	*How this review addresses*
1	Justification of the review's importance	Introduction establishes PE's clinical burden in India (8–10% incidence, ~21% of maternal deaths) and the diagnostic-infrastructure gap that motivates a low-cost biomarker.
2	Statement of concrete aims/questions	The introduction states 3 explicit review questions (non-renal mechanisms, diagnostic/prognostic value, and practical utility of UA testing).
3	Description of the literature search	Search Strategy names the databases, search terms, Boolean logic, date ranges, and most recent update; Eligibility Criteria and Study Selection Process describe inclusion/exclusion logic. Exact record counts are explicitly disclosed as not tracked, rather than fabricated or omitted silently.
4	Referencing	33 references are cited at the specific claims to support, spanning mechanistic, cohort, meta-analytic, and guideline sources.
5	Scientific reasoning	Causal language is consistently hedged (e.g., "consistent with, though not definitive proof of"); Section X explicitly presents conflicting evidence and counter examples rather than only confirmatory findings.
6	Appropriate presentation of data	Tables 1 and 2 and Figures 1–3 summarize study characteristics and comparative data in formats that mirror, rather than embellish, the cited sources; uncertain or unreported values are labelled "N/S" rather than inferred.

pregnant women. Thus, it is evident that the pathogenic role of uric acid is increasing. In the non-pregnant population hyperuricemia is an independent predictor of cardiovascular and renal disease in both the general population and in subjects with chronic hypertension.[3] Consequently, no single serum UA value can be interpreted independently of gestational age, and the cutoff values considered (Section VIII) must be evaluated with respect to this UA levels. In the pregnant patient with PE, GFR decreases from normal levels (although not necessarily to within non-pregnant ranges before definitive impairment) and reduced urate clearance likely contributes to part of the increase in serum UA. Other non-renal factors (listed below) are hypothesised to play a contributing, perhaps major, role in some of the elevation in serum UA in this setting, rather than acting as a replacement for the presumed reduced GFR induced urate clearance.

UA elevation in PE: evidence for non-renal contributions

The elevation of UA in PE has commonly been thought to result mainly from diminished renal clearance, the prevailing presumption being that limited glomerular filtration can hinder urinary secretion of urate. This assumption is questionable on several counts.

- UA levels were reported to increase by days to weeks before there was evidence of impaired renal function on tests of creatinine or blood urea nitrogen in some groups of patients who developed PE.[3,7-10]
- PE patients with no evidence of impaired renal function have consistently demonstrated significantly greater levels of UA than in non-hypertensive patients,[8-16]
- Compared with tests of renal function, UA has proven to be more discriminatory for PE than were creatinine, blood urea nitrogen, or cystatin C.[10]

These observations imply that factors other than a reduced renal clearance of UA contribute to UA elevation in PE.

Placental Ischaemia and Xanthine Oxidase Activation

One suggested non-renal mechanism centres around the enzyme Xanthine Oxidoreductase (XOR), which is known to be present in relatively high concentrations in the human placenta. Under normal physiological circumstances, XOR acts mostly as a dehydrogenase (XDH), utilizing NAD+ as an electron acceptor in the two stage oxidation of hypoxanthine to xanthine and xanthine to uric acid.[4] Under conditions of ischemia re-perfusion stress, some XOR is converted to its oxidase form (XO), which utilises molecular oxygen instead of NAD+, generating superoxide radicals (O-) in the production of each uric acid molecule.[4] This provides a rational mechanistic link between the presence of placental ischemia, an elevated level of UA, and oxidative stress, two common features of PE.20-24

In initial work, Roberts et al. suggested a role for UA in PE induced endothelial dysfunction through nitric oxide depletion.[5] Bainbridge et al. demonstrated that UA was linked to activation of vascular smooth muscle cells and development of hypertensive response.[3] Yanglem et al. reported a study in an Indian cohort on the activity of XO, UA, Urea, Creatinine, and antioxidant status in 50 PE cases and 25 controls at RIMS, Imphal.[16] PE group had increased activity of XO and higher UA with normal urea and creatinine, as seen with non-renal XO-mediated increase in UA.[24]

NLRP3 Inflammasome Activation and Immune-Metabolic Amplification

It's also proposed that a second way the immune system could connect with the metabolism of the UA, i.e, UA could act as DAMP at some levels, inducing NLRP3 inflammasome activation in the cytoplasm (phagocytes, macrophages, dendritic cells and macrophages) upon cell damage, sterile or infectious.[6-26] NLRP3 activation triggers cleavages procaspase-1 to caspase-1, which cleaves proIL-1 and proIL-

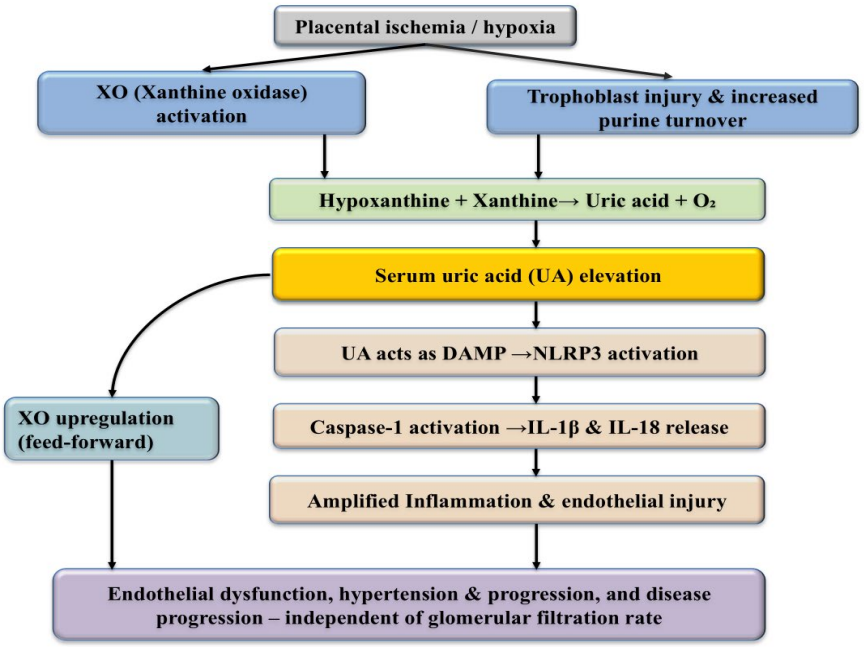

Fig. 1: Proposed non-renal pathways contributing to hyperuricemia in preeclampsia (see Section V for additional pathways not depicted, including angiogenic imbalance, complement activation, and immune dysregulation).

18. The production of inflammatory IL-1 and IL-18, then, theoretically, causes XO to produce UA again.[6,8-22]

Shirasuna et al. noticed increased NLRP3 expression, increased levels of IL-1 and IL-18, and evidence of trophoblast inflammation in PE compared with normal pregnancy.[6] Khaliq et al. presented a group of possible mechanisms leading to placental ischemia, with XO and NLRP3 induced by UA as components. They noted that the causal sequence remains insufficient to establish clearly the causality relationships between all those pathways.[7] In another study, Chen et al. observed that UA was more strongly correlated to PE compared to cystatin C (84 PE, 88 Controls).[10] This supports but does not prove an important role of a non-renal contribution to UA levels in PE. Khaliq et al. emphasized that although hyperuricemia is strongly associated with preeclampsia, its precise pathogenic role remains uncertain and requires further investigation.[7]

Additional Proposed Mechanistic Pathways

Angiogenic Imbalance (sFlt-1 and PlGF)

Soluble fms-like tyrosine kinase-1 (sFlt-1) is an antiangiogenic factor, which neutralises vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) by binding both mediators; in PE, levels of sFlt-1 are increased, whereas PlGF levels are decreased, leading to an increased ratio sFlt-1/PlGF that is commonly accepted as an index of the altered angiogenicity causing PE-induced endothelial dysfunction .[30] The increased release of sFlt-1 is probably triggered by the increased production by the placenta (similar to XO) following ischaemia, implying an overlapping regulatory mechanism . This is analysed in more detail in Section VII, where UA is compared directly to sFlt-1 and PlGF.[12]

Endothelial Dysfunction

It is thought that endothelial dysfunction as a systemic condition is the key unifying feature in PE, connecting placental abnormality with the maternal syndrome of hypertension, proteinuria, and multisystem dysfunction. UA (via less availability of nitric oxide) and sFlt-1 sequestration of VEGF might intersect in this endothelial damage pathway to explain the overlap seen among different mechanisms and their correlations with the severity of PE.[3, 20-30]

Complement Activation

Compensatory activation (high complement split products such as C5a and reduced complement regulatory protein expression) has been documented in PE and may contribute to the endothelial damage and potentiate the inflammatory cascade together with NLRP3 signalling. The role and mechanism of interaction between complement and urate-induced inflammasome activation are currently under active study and not a proven causal mechanism.[33]

Immune Dysregulation

PE has also been correlated with modifications in maternal immune tolerance, with changes in the function of regulatory T cells and a shift in favor of pro-inflammatory T-helper responses in the maternal-fetal interaction. These alterations in immunity may occur upstream or in parallel to the inflammasome induced feed forward amplification loop described in section IV; however, the causal balance or sequence of events leading to

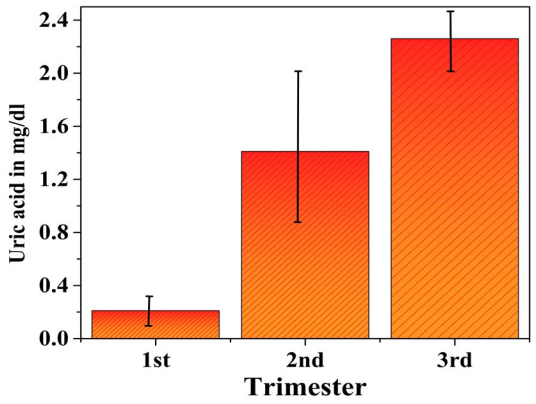

Fig. 2: Incremental increase in serum uric acid across gestation in preeclampsia relative to normotensive pregnancy. Data source: Bellos et al. 2020.[11]

the elevation in UA has not been firmly established, nor is this something that this review will attempt to solve.[20-22]

Diagnostic and Predictive Utility of Uric Acid Across Gestation

Diagnostic utility of UA for PE is differential over pregnancy, and this appears related to both the physiological adjustments to renal urate metabolism reviewed above (Section I) and the progressive placental damage. Consequently, rather than pooling the available evidence, this review by trimester, as suggested by avoiding the combination of predictive performance estimates throughout pregnancy. Bellos et al. reported that serum uric acid levels are consistently higher in women with preeclampsia than in normotensive pregnancies, with the difference becoming more pronounced as gestation advances.[11]

First Trimester

The average difference in the increase of UA in serum between the subsequent PE pregnancies and the normotensive pregnancies during the first trimester was low in the Bellos et al. meta-analysis that evaluated 196 studies and 39,540 pregnancies, +0.21 mg/dL (95% CI 0.06–0.35).[11] It is low as it cannot stand alone for the prediction of PE at this point, although it might still be an incrementally useful predictor as part of a multi-parameter risk score. The non-linearity between the levels of UA measured prior to 20 weeks and subsequent PE is evident in the large retrospective study by Yue et al. with a cohort of 44,609 pregnancies with a single foetus, with a sharp turning point around 240 mol/L, at which time renal parameters are normally functional.

Second Trimester

In the same meta-analysis, the mean incremental UA was greater, +1.41 mg/dL (95% CI 0.78-2.05) in the second trimester.[11] Colmenares et al. reported case-control results from 1,365 PE cases and 1,886 controls with a mendelian randomisation analysis, adjusted odds ratio of 1.21 (95% CI 1.11-1.33) per standard deviation increment in UA and the prospective subgroup with UA measured before 20 weeks had an odds ratio of 1.46 (95% CI 1.22-1.75) for later PE .[12] Although Mendelian randomisation may provide evidence of a plausible causal effect between genetically determined UA concentrations and PE risk, Mendelian randomisation results such as these may indicate association in a likely causal direction. Still, they cannot confirm causality, as pleiotropy or other unmeasured confounding could be responsible.[21]

Third Trimester

The difference between PE and normotensive pregnancies for UA was greatest in the third trimester, with a mean incremental increase of +2.26 mg/dL (95% CI 2.12-2.40).[11] This is consistent with the peak timing of placental ischaemic burden and – according to the physiology described in Section I – the trimester when renal urate clearance has already begun its decline back towards pre-pregnancy levels in normal gestation. For the selected studies, the ranges are sensitivity (67.3%–82.7%) and specificity (47.7%–70.7%).[23] Thus, UA provides a moderate level of diagnostic accuracy. However, in

Table 2: Comparative overview of serum uric acid and the sFlt-1/PlGF ratio as biomarkers in preeclampsia.

Feature	*Serum Uric Acid (UA)*	*sFlt-1 / PlGF Ratio*
Primary mechanism	Purine catabolism via xanthine oxidase; NLRP3-mediated inflammation; reduced renal clearance	Anti-angiogenic (sFlt-1) vs pro-angiogenic (PlGF) imbalance affecting VEGF signalling
Typical assay cost	Low — colorimetric/enzymatic assay, widely available on standard biochemistry analyzers	Higher — requires an immunoassay platform (e.g., ELISA or automated immunoassay analyzer)
Point-of-care feasibility	High—amperometric biosensor strips reported; salivary UA explored for rural settings[17-25]	Limited — emerging POC immunoassay platforms exist but are less widely deployed in low-resource settings.
Reported sensitivity/ specificity	≈67–88% / ≈48–93%, varying by cut-off and gestational age[8,11-23]	sFlt-1/PlGF ratio ≤38 reported with high negative predictive value (~99%) for ruling out PE within 1 week[31]
Best-supported clinical use	Adjunct triage marker; risk stratification alongside blood pressure and proteinuria	Short-term rule-out/rule-in tool in women with clinically suspected PE
Guideline incorporation	Not currently incorporated into major international PE guidelines as a standalone diagnostic criterion	Referenced in select international guidance (e.g., NICE) for short-term risk stratification[31]

Table 3: Studies using UA assessment where PE was independently confirmed by ACOG/ISSHP criteria. "N/S" indicates not specified in the source publication. Several Indian site reports[19,27-29]

STUDY / SITE	*Country*	*Design*	*PE (n) / Control (n)*	*Gest. Age*	*UA Cut-off*	*Performance*	*Renal Excl.*	*Quality Notes*	*Overall Study Appraisal (Informal)*	*Ref*
Bellomo et al. diagnostic accuracy of UA	Italy	Case-control	74 / 163	3rd tri.	5.2 mg/dL	AUC 0.955; Sn 87.7%; Sp 93.3%	Yes	Single-centre; strong effect size may not generalize	Moderate	8
Colmenares-mejia et al. Risk per unit UA rise	Colombia	Case-control + MR	1,365 / 1,886	Mixed	1 SD increase	adj. OR 1.21/SD; prospective OR 1.46	Partial	MR supports association, not definitive causality	High	12
Bellos et al. Global meta-analysis	Global (196 studies)	Meta-analysis	39,540 total	All tri.	Variable	Sn 67.3–82.7%; Sp 47.7–70.7%	Per study	High heterogeneity across pooled studies	Moderate	11
Le et al. UA in asian population	Vietnam	Cohort	205	3rd tri.	393 µmol/L	AUC 0.752; Sn 64.4%; Sp 79.5%	Yes	Moderate accuracy; single-site	Moderate	9
Chen & lian — UA vs renal markers	China	Case-control	84 / 88	Not spec.	Highest vs ctrl	Best AUC vs renal indices incl. cystatin C	Yes	Small sample; single-centre	Low	10
Piani et al. — UA/ creatinine ratio	Italy	Cohort	112	All tri.	UA/Cr ratio	Elevated in all trimesters; normal Cr confirmed	Normal Cr	The ratio approach adjusts for renal confound	Moderate	14
Baitha et al. — Patna medical college	India (Bihar)	Prospective case-control	250 / 250	3rd tri.	6.2 mg/dL	Acc 83.3%; Sn 72.4%; Sp 87.6%; PPV 85.3%	N/S	Large sample; single tertiary centre	Moderate	15
Yanglem et al. — RIMS Imphal	India (Manipur)	Case-control	50 / 25	Not spec.	Clinical Dx	Mean 8.82 vs 4.06 mg%; p<0.001	Yes	Small control group (n=25)	Low	16
Madaan et al. — Wardha rural hospital	India (Maharashtra)	Prospective, 2-yr	180 total	Mixed	5.06 mg/dL (salivary)	Accuracy 78.33%; salivary UA for rural PoC	Yes	Novel salivary approach; needs external validation	Moderate	17
Medical college kolkata — perinatal outcome	India (West Bengal)	Prospective	115	Not spec.	6.0 mg/dL	Majority >6 mg/ dL in PE; DM/CKD excluded	Yes	No matched control group was reported	Low	18
JLN medical college, Ajmer	India (Rajasthan)	Cohort	Not spec.	Not spec.	Not spec.	Higher UA is associated with severity/ poor prognosis	N/S	Sample size and exact statistics are not reported	Unclear	27
SCB medical college, Cuttack	India (Odisha)	Cross-sectional	1,200	Not spec.	>6 mg/dL	Highest mean UA (9.2±2.89) in severe PE	N/S	Large sample; severity-stratified	Moderate	28

STUDY / SITE	Country	Design	PE (n) / Control (n)	Gest. Age	UA Cut-off	Performance	Renal Excl.	Quality Notes	Overall Study Appraisal (Informal)	Ref
Bangalore medical college	India (Karnataka)	Cohort	Not spec.	Not spec.	Not spec.	Positive correlation between UA and BP	N/S	Exact sample size and statistics not reported	Unclear	[29]
Medical college Baroda, Vadodara	India (Gujarat)	Cohort	Not spec.	Not spec.	Not spec.	UA correlated with hypertension and outcome	N/S	Exact sample size and statistics not reported	Unclear	[19]

a cohort of women with documented normal renal function, Bellomo et al. Found higher accuracy values for UA using an AUROC at a cut-off of 5.2 mg/dL, with 87.7% sensitivity, 93.3% specificity, 92.4% positive predictive value, and 88.8% negative predictive value.[8]

Piani et al. Analysed the UA-to-creatinine ratio and observed this value to be raised in all three trimesters in PE, even in women who have normal creatinine levels.[14] Because of dividing by creatinine (i.e., attempting to consider any component from renal excretion of UA), the fact that this index is raised even after division suggests a component from other, i.e., non-renal, sources.

Comparison with Established Angiogenic Biomarkers: sFlt-1 and PlGF

SFlt-1/PlGF ratio is arguably the most validated combination biomarker in PE, and it has a place in global clinical guidelines. UA works by a different mechanism, has a different cost profile and evidence base than sFlt-1/PlGF, and these differences are listed in Table 2

Given its low cost and compatibility with point-of-care biosensor platforms, UA may be best positioned as a low-resource setting adjunct to clinical risk factors (blood pressure, proteinuria) rather than as a substitute for sFlt-1/PlGF where the latter is available. Unlike angiogenic indicators that directly represent placental vascular malfunction, UA reflects a combination of oxidative stress, renal physiology, placental ischaemia, and purine metabolism. In settings where sFlt-1/PlGF testing is inaccessible or unaffordable, UA-based triage may still provide incremental clinical value.

Variability in Diagnostic Cut-off Values

Suggested UA cut-offs for the diagnosis of PE vary widely across the literature we considered, from approximately 5.2 mg/dL.[8] to 6.0 mg/dL.[18] to 6.2 mg/dL[15] to site-specific cut-offs reported elsewhere in Table 1.

- Differences in population/ethnic background on baseline urate metabolism and renal handling;
- Gestational age at which the sample was taken; due to the trimester-related changes in physiology described in Section I;
- Methodological differences in test assays (colorimetric versus enzymatic electrochemical versus salivary biosensor assays may vary in their calibration and reference ranges);
- PE severity in the population of the study (samples enriched in severe PE are often associated with a mean higher UA and higher best estimate cutoff values)
- Methodological differences in study design (was formal exclusion of impaired renal function performed and matching of control groups for gestational age).
- Given the high variability in proposed UA cutoffs for PE diagnosis in the literature, a universal cutoff may not be ideal, and validated population-specific cutoffs may be needed before wide-scale implementation of UA-based point-of-care diagnostics even in India.
- IX. Documented Patient Data: International and Indian Clinical Populations

Table 3 is an inclusive tabulation of some clinical studies in which PE was independently validated by ACOG or ISSHP criteria; included studies were conducted in Italy, Colombia, the worldwide meta-analysis population, Vietnam, China, and at various Indian locations. Variables abstracted included: study design; gestational age at study measurement; patient population characteristics; the exclusion criteria for patients with renal disease; and remarks about study quality. The site reports below elaborate on several case examples where specific quantifiable data were provided.

Italian cohort by Bellomo et al.[8] and Vietnamese cohort by Le et al.[9] are comparable in the criteria used for the diagnosis but gave dissimilar AUROCs (0.955 vs. 0.752) and optimum thresholds (5.2 vs. 393 mol/L [~ 6.6 mg/dL]), highlighting the issue of threshold diversity that we also noted in Section VIII, and the importance of context-specific calibration rather than extrapolating thresholds between settings.

Bihar, India — Patna Medical College

A study by Baitha and co-workers included 500 pregnant women at the third trimester (PE; n=250; normotensive, n=250) from a tertiary care hospital of Patna, Bihar, using a case-control design. At a cut-off level of 6.2 mg/dl, values for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 72.4,

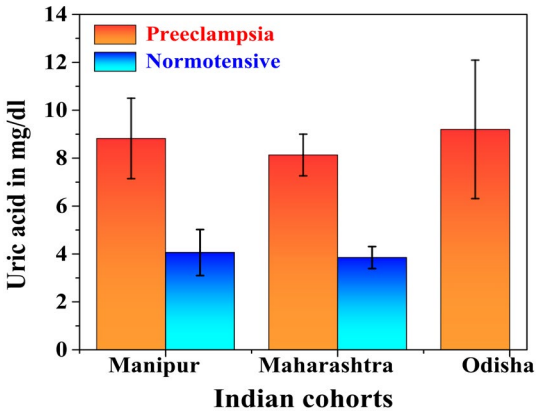

FIG. 3: Serum levels of uric acid at baseline for selected Indian cohort studies with available mean and standard deviation for Preeclampsia compared to normotensive pregnant women.[16-28]

87.6, 85.3, 80.5, and 83.3%, respectively. A good correlation between urate levels and diastolic blood pressure was also reported ($r=0.606$, $p<0.05$).[15]

Manipur, India — RIMS Imphal

In Yanglem et al the study consisted of 50 patients with PE and 25 healthy normotensive subjects. For example, the UA value for their PE group is 8.82±1.68 mg%, and that for the control group is 4.06±0.96 mg%. Mean serum urea and creatinine were not significantly different between the two groups, suggesting increased purine breakdown from ischaemia and not from kidney damage. A study limitation was the smaller size of the control group (n~25).[16]

Maharashtra, India — Rural Hospital, Wardha

In a two-year (2019-2021) prospective study of 180 women, salivary UA biosensor technology was used for the screening of PE in a clinical setting. In patients with severe PE, the mean UA was 8.13 ± 0.87 mg/dL, whereas in those with mild PE, it was 6.23 ± 0.76 mg/dL. In the control group, the mean serum UA was 3.85 ± 0.46 mg/dL. Saliva UA could predict eclampsia, HELLP syndrome, and acute renal failure with high sensitivity (78.33%). Salivary UA may be a useful method to be used in a quick, economic, and non-invasive screening protocol, but external validation in a greater cohort is still needed to make it widely available.[17]

West Bengal, India — Medical College Kolkata

115 proven PE subjects underwent the study, including neither diabetic nor thyroid patients, or the patient having any prior renal failure.[18] PE was associated mostly with UA above 6 mg/dL. Mean age of study participants was 28.90 ± 5.15 years and is representative of the reproductive age group affected by PE in India.

As depicted in Fig 3, results from different geographically diverse parts of India showed high mean serum UA in PE when compared to normotensive pregnancy, although actual levels, methods of estimation, period of gestation, and directly matched controls were variable among different centres.

Conflicting Evidence and Limitations

However, the evidence presented in this review is mixed, and there are several major caveats which must temper optimism for clinical implementation of UA as a biomarker: Sensitivity and specificity of UA are moderate, rather than high, in pooled analyses (Sn 67.3-82.7%; Sp 47.7-70.7% [11-23]); therefore, a substantial proportion of patients with PE could be missed, and a meaningful proportion of women without PE could be misclassified, should UA be applied as a sole diagnostic marker. The range of reported diagnostic performance (AUROC 0.955 in Bellomo et al.[8] vs. 0.752 in Le et al.[9], for example) is wide, and individual studies which are centre based with high impact values cannot be generalised to wider populations. Several site-specific Indian reports.[19, 27-29] included here did not provide full sample size and/or statistical data in the respective documents, hence reducing the power of any single report to stand alone. UA has limited specificity, being affected by gout, chronic kidney disease, use of diuretic agents, dehydration, purine content of the diet, and other metabolic disorders, all of which will need to be addressed and excluded in clinical management where possible. As renal urate excretion rates fluctuate in pregnancy itself (Section I), UA cannot be evaluated using non-pregnant reference values and, to date, most jurisdictions - including a large proportion of India - lack gestation-age adjusted and local standards. Head-to-head comparison of UA screening versus sFlt-1/PlGF screening was not performed in any study included in this review in a prospectively comparative design; the discussion on comparative value presented in Section VII is thus inferential, rather than evidence-based from a specific trial.

This is a narrative and not a systematic review and has not included formal risk-of-bias and certainty-of-evidence assessment (see Materials and Methods), with the findings and conclusions presented representing a general synthesis of current evidence. Overall, the arguments presented indicate that UA has the greatest utility as an adjunctive or complementary measure – perhaps of most value in resource-limited regions where access to costly angiogenic biomarkers may be restricted – rather than as a diagnostic tool for use on its own, nor as a means of substituting the use of existing clinical criteria and biomarkers.

Clinical Implications and Future Directions for Point-of-Care Diagnostics

It is possible, based on the convergent mechanistic, epidemiological and Indian clinical data that reviewed here that a not inconsiderable fraction of the UA rise in PE could have its genesis outside of overt primary kidney damage (although the contribution from kidney function as conditioned by gestation - as reviewed in Section I - should also be assumed likely), but coexisting with the other pathways outlined in the foregoing text. If this is true, this alternative conception could lead to the deployment of UA measurement early in

the diagnostic sequence – as a risk stratified, or a triage, rather than as a marker of advanced kidney disease once PE is evident. The diagnostic threshold for elevated UA across the reports considered in the review, including those in India, varies broadly from about 5.2-6.2 mg/dL, although it should be remembered that these values cannot be assumed to be interchangeable between population sets, as explored more thoroughly in Section VIII herein.

Amperometric biosensors exploiting the enzyme uricase provide a simple, low-cost technology capable of on-demand measurement of blood UA, and similar devices are already used to test urine in patients with gout or blood glucose levels. .[25] Salivary measurement, such as is possible in the Wardha population, may further improve access in rural settings where measurement of blood UA cannot be readily performed in light of blood drawing technology.[17] It seems plausible that such a pathway could consist of a training programme where such a UA biosensor is used by a trained community health worker (ASHAs and ANMs in India) to screen every patient at every visit with a referral for measurement of blood pressure and dipstick urine testing of urine on detection of an abnormal value. Inexpensive, low-cost point-of-care biosensors could provide useful triaging capacity when the level of precision required and cost considerations dictate that it is worth undertaking a large number of tests to pick up a small number of potential patients with PE. However, before this may reasonably be put into practice, a cost–effectiveness assessment would need to be conducted of the comparison between current practice and utilization of the biosensors and formal testing of the latter to demonstrate it as a useful clinical tool, not just as has been demonstrated, a reasonable predictor.

CONCLUSION

The collective evidence reviewed supports the idea that the increased serum UA in preeclampsia represents more than just an artefact of renal compromise and may reflect an ischaemic, oxidative, inflammasome-driven placental stress response, mediated by xanthine oxidase-dependent purine catabolism, superoxide production and NLRP3-mediated inflammatory amplification, perhaps in combination with associated features such as angiogenic imbalance and endothelial dysfunction. This reading should be regarded as an informed hypothesis with several supportive lines of evidence.

More high-quality prospective validation studies, including population- specific threshold validation, are required for routine implementation, alongside full economic cost-effectiveness analyses. The overall picture derived from reports on several regions of India (Bihar, Manipur, Maharashtra, West Bengal, Odisha, Rajasthan, Karnataka and Gujarat), as well as from various parts of the world (Italy, Vietnam, China, and Colombia), are broadly consistent with a relationship between elevated serum UA and PE, although significant variation in absolute levels and diagnostic value is evident between different study sites.

With an incidence of PE of 8-10% in India and hypertension being associated with approximately 21% of maternal mortality, the need for low-cost and easily accessible screening tests continues to remain high. The mechanistic and clinical data presented in this review support the notion that point-of-care UA biosensors could potentially be developed as an additional screening test that complements (not replaces) the monitoring of blood pressure, measurement of proteinuria, and, where appropriate, measurement of angiogenic markers such as sFlt-1/PlGF. Still, before the potential broad implementation of these tests, further carefully conducted validation studies and validation of threshold cutoffs specific to the population are necessary, as well as complete cost-effectiveness studies.

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