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ORIGINAL ARTICLE

Maternal Serum Cyclophilin A: A Predictive Biomarker of Preeclampsia in South Indian Women

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Abstract

Background Serum Cyclophilin A (CyPA) is a 20 KD chaperone protein, secreted in response to oxidative stress and has an important role as mediator of inflammation. CyPA has been related to Preeclampsia (PE) and implicated as its potential biomarker.

Objectives To analyze serum Cyclophilin A levels in preeclamptic women and compare it with healthy pregnant women, in South India. We aimed to look for its validity as a predictive biomarker for PE.

Methods This is a prospective cohort study, conducted in pregnant women attending the OPD of a private medical college hospital in Salem. Maternal serum CyPA levels were assessed in PE and healthy pregnant women in their 2nd trimester (20–26 weeks) and repeated again in the 3rd trimester of PE women.

Results Among 120 pregnant women recruited for the study, 60 were preeclamptic and 60 were healthy pregnant women. Higher serum CyPA levels were observed in PE group (34.58 ± 5.53 ng/ml), compared to healthy pregnant women (7.41 ± 7.7 ng/ml), $p < 0.001$. CyPA also had good discriminating ability between PE & healthy pregnancy, (AUC = 0.971, 95% CI 0.932–1.00), with high sensitivity (98.33%)and specificity (98.33%).

Conclusion CyPA levels were markedly increased in preeclampsia, and could be a novel biomarker of preeclampsia.

Keywords Cyclophilin A · Preeclampsia · Indian women · Second trimester

Introduction

Preeclampsia (PE) is a pregnancy specific hypertensive disease affecting 8–10% of pregnant women in India, and is leading cause of morbidity and mortality all over the world. It is a multisystem disorder characterized by exaggerated maternal systemic inflammatory response to pregnancy. In preeclampsia, there is excessive activation of immune system with increased levels of systemic proinflammatory cytokines like TNF-α, IL-6, IL-1β and IL-18 resulting in the placental dysfunction and maternal systemic complications [1]. TNF-α and other circulating factors present in PE can induce oxidative stress in endothelial cells [2]. The abnormally upregulated immune system results in inappropriate trophoblast invasion in myometrium and insufficient spiral arteries remodelling causing placental ischemia, which could result in vascular inflammation and endothelial dysfunction [1].Maternal systemic inflammatory response in combination with oxidative stress could have a pivotal role in the etiology of PE.

Cyclophilin A (CyPA) is an intracellular and extracellular ubiquitous protein belonging to the immunophilin family, having peptidyl prolyl isomerase activity and was first recognized as a cytosolic binding protein of immunosuppressant drug Cyclosporin A [3, 4]. CyPA is a strong chemotactic agent attracting T cells, monocytes, eosinophils & neutrophils and is capable of eliciting an inflammatory response [5]. CyPA is secreted by vascular smooth muscle cells, endothelial cells and macrophages, in response to inflammatory stimuli like infection, oxidative stress and hypoxia

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[5, 6]. There is evidence for elevated CyPA in patients presenting with inflammatory diseases like chronic kidney disease, Diabetes mellitus and cardiovascular diseases [6–8]. Hypertensive males had higher CyPA levels compared to non-hypertensives, with their BP correlating well with CyPA levels [9].

Currently, CyPA being an inflammatory mediator has been studied in serum, placental tissue and cord blood of preeclamptic women, in different countries. During recent times, there are few studies implicating elevation of maternal serum CyPA levels in preeclampsia, with efforts being made to identify its role in the underlying mechanisms of maternal syndrome [10, 11]. Existing evidence point towards the involvement of CyPA in development of PE and this study attempts to identify the association in Indian population.

To the best of our knowledge, there are no similar studies on serum Cyclophilin A levels in preeclampsia, conducted in Indian population. Our aim was to investigate, whether its levels increased among preeclamptic Indian women, as early as 2nd trimester, when compared to normal pregnancies and to evaluate its efficiency in predicting the development of preeclampsia.

Materials and Methods

This prospective cohort study, has been conducted for a period of one and half years, from March 2021 to September 2022. The study was approved by Institutional Ethical Committee of a private medical college hospital. Assuming that 10% of subjects in the population will develop pre- eclampsia, and a population size of 100, the study would require a sample size of 90 for estimating the expected proportion with 20% precision relative to the expected proportion (i.e. $0.2 \times 0.1 = 2\%$ absolute precision) and 95% confidence [12].

Study Participants

The participants enrolled for our study included preeclamptic and healthy pregnant women, in 2nd trimester of pregnancy (20–26 weeks), attending antenatal OPD of the hospital. The PE women were diagnosed in their 2nd trimester and both groups were followed up till delivery.

Preeclampsia was diagnosed in pregnant women presenting with new onset hypertension (systolic BP ≥ 140 mm Hg and diastolic BP ≥ 90 mmHg), after 20 weeks of gestation in a previously normotensive patient, and proteinuria, using FOGSI guidelines [13]. Patients having urine protein > 300 mg/day or dipstick reading > 2 +, were recruited for the study.

We recruited already diagnosed preeclamptic women in 2nd trimester of pregnancy for our study, and measured serum Cyclophilin A levels, in both the trimesters. The comparison group included normal pregnant women in 2nd trimester of pregnancy. Pregnant women with history of chronic hypertension, gestational diabetes mellitus, other pre-existing diabetes, renal, cardiovascular, haematological diseases, hepatitis, or any other medical illnesses complicating pregnancy were excluded from the study. We ruled out and excluded preeclamptic women with h/o recurrent abortions and known connective tissue disorders.

Participants' information such as demographic details and medical history were procured from their health records. Informed consent was obtained from all participants volunteered, after explaining to them the purpose of study, possible risks and benefits.

Maternal Fetal Status

Pregnant women in both the groups were followed up till delivery and maternal/ fetal status and baby birthweights were noted.

Specimen Collection

After overnight fasting, 5 ml of blood was collected from median cubital vein of the participants. Serum was separated and around 1 ml was used for analysis of biochemical parameters & remaining serum stored in eppendorfs at −20 °C for analyzing the Cyclophilin levels. Repeat blood samples were collected in the 3rd trimester of pregnancy in PE women, for estimating CyPA and other parameters.

Laboratory Analysis

Quantitative analysis of serum CyPA was done by sandwich Enzyme Linked Immunosorbent Assay technology using Finetest ELISA kit (Wuhan Fine Biotech Co.,Ltd), in Robonik ELISA reader. Serum HsCRP had been estimated by Nephelometric method, using PA 52- Nephelometer and uric acid by Uricase method, in Fully automated analyzer EM200. Urine protein was assessed by urine dipstick method.

Statistical Analysis

Continuous and categorical data were summarized as means and proportions respectively, at 5% level of significance. Descriptive statistics of Serum CyPA, HsCRP and uric acid levels were compared among healthy pregnant and preeclamptic women in 2nd trimester of pregnancy and analysed using student's independent "t" test. Normality distribution of quantitative data was tested by Shapiro Wilk's test. In PE women, blood levels of all three parameters in 2nd trimester were compared with that of 3rd trimester. Pearson's correlations were computed to identify correlations of CyPA levels

with hsCRP, uric acid, systolic and diastolic BP and also with baby birthweights. Associations were established using odds ratio (& adjusted odds ratio), computed by binomial logistic regression method.

Using Receiver operating characteristic (ROC) analysis, we tried to determine the ability of CyPA to discriminate PE women from normal pregnant women without preeclampsia, and cut-off values were established. Statistical analysis of data was performed using Jamovi version 2.3.18 software and SPSS software version 26.

Results

Totally 120 pregnant women in their 2nd trimester of pregnancy (20–26 weeks gestation), were enrolled in the study. Among them 60 were healthy pregnant women and remaining 60 were pregnant women diagnosed to have preeclampsia. Overall mean age of participants was 25.86, mean age of preeclamptic and healthy pregnant women being 25.87 ± 3.66 and 25.85 ± 3.17 respectively. The demographic characteristics and biochemical parameters are displayed in Table 1.

Cyclophilin A & Other Parameters In 2nd Trimester

In PE women, mean serum CyPA level was 34.58 ± 5.53 ng/ml, while that in healthy pregnancy it was 7.41 ± 7.7 ng/ml, mean difference being 27.27 ng/ml. CyPA was significantly higher in PE women compared to normal pregnant women, $p < 0.001$(Table 1). Serum CyPA had a strongly positive correlation with systolic and diastolic BP, with Pearson's correlation coefficients (r) of 0.718 and 0.705 respectively, $p < 0.001$ (Table 2).

Similarly, serum hsCRP, which is another inflammatory marker was assessed in both the groups. Mean hsCRP was 6.18 ± 1.61 mg/l in PE women and 4.42 ± 1.86 mg/l in healthy pregnant women. The mean difference was 1.76 mg/l and it showed significant elevation in PE ($p < 0.001$). Uric acid was also elevated in PE group ($p < 0.001$), compared to healthy pregnant group (Table 1). Serum CyPA positively correlated with hsCRP (r = 0.446) and uric acid ((r = 0.531), $p < 0.001$ (Table 2).

Table 2 Correlation of Cyclophilin A with other parameters

Parameters	Correlation coefficient (r)	Sig (2 tailed)
Cyclophilin A with		
Uric acid	0.531	< 0.001
hsCRP	0.446	< 0.001
Systolic BP	0.718	< 0.001
Diastolic BP	0.705	< 0.001
Birth weight	− 0.276	0.002

Binomial logistic regression

Biochemical markers such as cyclophilin A, uric acid and hsCRP were found to have positive associations with PE. The regression model (3 markers) was statistically significant, $\chi 2 = 154$, $p = < 0.001$ and it explained 96.3% (Nagelkerke $R^2 = 0.963$) of PE occurrence, among pregnant women. Increase in cyclophilin A had association to increased likelihood of PE by a factor of 1.28, which was significant ($p = 0.002$), even after adjusting for hsCRP and uric acid levels (Table 3).

Cyclophilin A and Other Parameters In 3rd Trimester

All the participants in PE group were followed up till the 3rd trimester. Significant increase of 21.73 ng/ml in the mean CyPA levels was observed in 3rd trimester of PE pregnancies, as compared to their levels in 2nd trimester, $p = 0.000$ (Table 4, Fig. 1). Since serum CyPA was quite low in normal healthy pregnant women in 2nd trimester, we did not repeat the CyPA test in the 3rd trimester. HsCRP & uric acid levels didn't show any significant change.

Table 1 Baseline characteristics of the variables among 2nd trimester healthy pregnant and preeclamptic women

S. No	Parameters	Healthy pregnancy (Mean ± SD)	Preeclampsia (Mean ± SD)	*p*-value
I	Socio demographics Age (yrs)	25.85 ± 3.17	25.87 ± 3.66	0.979
II	Systolic BP	108.50 ± 11.17	149.92 ± 10.44	< 0.001
III	Diastolic BP	71.67 ± 6.55	94.250 ± 6.3	< 0.001
IV	Cyclophilin A (ng/ml)	7.41 ± 7.7	34.58 ± 5.53	0.000
V	HsCRP (mg/l)	4.42 ± 1.86	6.18 ± 1.61	0.000
VI	Uric acid (mg/dl)	4.02 ± 0.6	6.56 ± 1.29	0.000
VII	Baby birthweight (kg)	3.31 ± 0.36	2.98 ± 0.45	< 0.001

levels ≥ 26.2 ng/ml, was low compared to the babies born to mothers with lower CyPA levels, $p < 0.001$.

Discussion

We have analyzed the maternal serum CyPA levels in PE and healthy pregnant South Indian women, in their 2nd trimester of pregnancy (20–26 weeks) and had followed them up, till childbirth. There are a few studies available in literature that have identified increased Cyclophilin A (CyPA) levels in PE, but to the best of our knowledge, there are no similar studies done in India. There was a remarkable increase in CyPA levels in PE, when compared to healthy pregnancies.

PE is an oxidative stress mediated inflammatory disease of maternal endothelium [1], though the exact mechanisms are unclear. In PE, there is insufficient trophoblast invasion leading to poor placentation and the oxidative stress in placenta releases factors into maternal circulation, resulting in maternal systemic inflammatory response & endothelial dysfunction, leading to the clinical signs of PE [14]. Haoyue Hu et al. have found that CyPA could inhibit MMP-2/9 expression in mouse placenta and HTR8/SVneo cells, thereby altering the migration and invasion of trophoblasts [15].

CyPA is an ubiquitous protein present intracellularly and secreted from the cells in response to Reactive Oxygen Species (ROS) [16–18]. Extracellular CyPA can stimulate both endothelial cells (EC) and vascular smooth muscle cells (VSMC), to release proinflammatory signals like VCAM-1 and E-Selectin [19]. VCAM-1 stimulates the adhesion of lymphocytes, monocytes, eosinophils & basophils to the vascular endothelium. CyPA is a chemoattractant and it interacts with leukocytes via CD147 receptors. At the sites of inflammation, CyPA -CD147 interaction is very important for recruitment of leukocytes, thus contributing to the inflammatory response [20]. In Han Chinese women, an association between CyPA genetic polymorphisms rs3735481, rs9638978 and greater risk for severe PE had been reported, along with increased placental expression of CyPAin severe PE [10]. While blood CyPA levels showed a rise, the cord blood levels were low, in severe PE women [21, 22].

Our study results have depicted a significant increase in maternal serum CyPA levels among 2nd trimester PE women, in comparison with healthy pregnant women. CyPA being a proinflammatory cytokine, exhibited robust association to PE development. In PE women, when CyPA test was repeated in 3rd trimester, there was a further significant increase, from that of 2nd trimester. This finding indicates the progressive increase in CyPA levels with increasing gestational age, in PE. CyPA could probably have an essential role in development and progression of PE, which has to be investigated in detail, by studies in larger populations.

Likewise Celik et al. [11] have identified an early second trimester increase in CyPA levels, before the occurrence of PE symptoms. According to them, CyPA levels were significantly increased in early onset PE, compared to that of late onset PE. In concordance with our study, Wenjuan Sun et al. have also reported high CyPA levels in early onset PE than that of healthy pregnancies ($p < 0.001$) [10]. Wang et al. have reported that 1st trimester CypA levels were increased in women developing complicated pregnancies like PE, Gestational Hypertension (GH) and Gestational Diabetes Mellitus (GDM) [23].

As per our findings, 2nd trimester maternal serum CyPA could be a good predictive biomarker for PE, while its utility as an early biomarker needs further exploration, by assessing its levels in the 1st trimester of pregnancies. Similarly, Celik et al. [11] have identified that early 2nd trimester maternal serum CyPA may have a good predictive value, in assessing the later development of PE. Findings of Wang et al. [23] have further emphasized the significance of circulating CyPA as a potential marker of PE, as well as other pregnancy complications like GDM and GH.

In our study serum levels of hsCRP which is an inflammatory marker, were increased in PE women compared to the normal pregnant women. Serum hsCRP also positively correlated with CyPA levels ($p < 0.001$). Likewise Wang et al. have reported serum CyPA to be closely related with CRP levels [15]. Uric acid, which is a routinely used investigation in the assessment of PE, was increased in PE compared to healthy pregnant women ($p = 0.000$). In PE women, along with CyPA, there was also rise in levels of the inflammatory marker hsCRP.

Limitations of the Study

Sample size was small and pregnant women developing PE later than 26 weeks were not included in our study. CyPA levels were not analyzed in 1st trimester of all participants & in 3rd trimester of normal pregnant women. The relationship of CyPA with maternal, neonatal morbidity or mortality have not been studied in detail.

Future Scope of this Biomarker

Cyclophilin A could have a promising role as biomarker for early screening and diagnosis of pre-eclampsia. It could be used for monitoring and assessing severity of PE, as well as its prognosis. Higher levels could have association with adverse maternal/ fetal outcomes like preterm delivery, maternal organ damage, fetal growth retardation and still births.

Conclusion

CyPA which is an inflammatory mediator could have a major role in the pathogenesis and progression of PE. Maternal serum CyPA levels showed a consistent increase in both second and third trimesters of Preeclampsia, compared to normotensive women. CyPA could be used as a valuable predictive biomarker for PE, but further prospective studies in first trimester of pregnancy, would help us establish its utility as an early screening test for PE. Its association with severity of PE and maternal/ fetal complications needs further investigations, thus extending the future scope of this study.

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Declarations

Conflict of interest Authors declare no conflict of interest.

Ethical Approval The study was approved by Institutional Ethics Committee (IEC) of Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals, Salem.

Human and Animal Rights The study was performed on human participants, in compliance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Written informed consent was obtained from all the participants who volunteered to take part in the study.

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