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A LONGITUDINAL STUDY OF BIOCHEMICAL VARIABLES IN WOMEN AT RISK OF PRE-ECLAMPSIA AND ROLE OF SEROTONIN

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ABSTRACT

Background: A multi-system disorder that typically occurs after 20 weeks of pregnancy in a woman with normal blood pressure previously is called preeclampsia. In preeclampsia patient suffer from new-onset hypertension and proteinuria.

Objective: To evaluate the variations in key biochemical variables in women at risk of preeclampsia and to investigate the specific role of serotonin in the onset and progression of this disorder.

Methodology: This prospective longitudinal study was conducted at Swat Medical College and its affiliated Hospitals from January 2022 to January 2023. A total of 195 pregnant women, deemed high-risk for preeclampsia based on clinical history and initial screening, were recruited for the study. At the initial visit (first trimester), demographic data and medical histories were recorded. Blood pressure measurements were taken and blood samples were collected for baseline biochemical analyses. Participants underwent scheduled follow-up visits in the second trimester and third trimester. At each visit, blood pressure was monitored, and additional blood samples were collected to measure biochemical variables of interest.

Results: There is an increase observed in soluble fms-like tyrosine kinase-1 (sFlt-1) which may indicate heightened endothelial dysfunction as there is progression in pregnancy. There s a gradual increase in levels of uric acid and creatinine which reflects renal stress commonly associated with advancing gestation. Rise in levels of serotonin in increments throughout trimesters suggests a progressive physiological adaptation or potential role in vascular regulation during pregnancy.

Conclusion: Our study contributes to the understanding of biochemical dynamics specifically highlighting the role of PlGF, sFlt-1, uric acid, creatinine and serotonin in the progression of preeclampsia. Hence these biomarkers are very important in the early diagnosis and treatment of those

pregnant women who are at risk of developing preeclampsia thus contributing to the understanding of pathophysiology of the condition along with helping in development of targeted therapeutic strategy.

Keywords: Preeclampsia, Biochemical markers, High-risk pregnancy

INTRODUCTION

A multi-system disorder that typically occurs after 20 weeks of pregnancy in a woman with normal blood pressure previously is called preeclampsia.[1] In preeclampsia patient suffer from new-onset hypertension and proteinuria. It also causes end-organ dysfunction such as thrombocytopenia, impaired liver function, renal insufficiency, pulmonary oedema and cerebral symptoms or visual impairment. The aetiology of preeclampsia is still unknown although it is believed that factors involved in it are related to maternal as well as fetus.[2]

Preeclampsia affects almost 5-10% of pregnancies globally. Its incidence varies worldwide. It is one of the major reasons behind maternal and perinatal morbidity and mortality globally.[3] It can cause severe complications i-e eclampsia (seizures), HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), placental abruption, and long-term maternal cardiovascular disease. Preeclampsia can affect fetus by causing restriction of intrauterine growth, pre mature birth, and stillbirth.[4]

For the improvement of maternal and fetal outcomes, early diagnosis and treatment of preeclampsia is very essential. Due to variability in its clinical presentation, it is difficult to identify which women will have this condition in the future.[5] To predict preeclampsia, multiple biochemical markers have been studied for their ability to diagnose it which includes 'placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), uric acid, and liver enzymes'.[6] Different aspects of pathophysiology of preeclampsia are reflected by these markers such as endothelial damage, oxidative stress, and placental dysfunction.[7]

Serotinin, a biogenic amine that works as a neurotransmitter in central nervous system. It is also a vasoactive agent in peripheral tissues. It is less studied but emerging evidence suggests that it is considered one of the important factors in the pathogenesis of preeclampsia. Its role in cardiovascular diseases is documented well. It also plays a role in vascular tone regulation, platelet aggregation and proliferation of smooth muscle cell.[8]

There are significant changes observed in serotonin levels and metabolism in pregnancy.[9] It can affect both maternal and fetal physiology as it is produced in the placenta. Investigations suggest that the vascular tone of the uteroplacental circulation can be modulated by serotonin which is important for maintenance of adequate blood flow to the placenta and the fetus.[10,11,12] Many pregnancy complications have reported abnormal signalling of serotonin which also includes preeclampsia.[13]

In this context, the relationship between serotonin and the vascular system could contribute to the fact that changes in the levels of serotonin or its signalling pathways could be responsible for the development of preeclampsia. The present investigation aims to evaluate the variations in key 'biochemical variables in women at risk of preeclampsia' and to investigate the specific role of serotonin in the onset and progression of this disorder.

MATERIALS AND METHODS

This prospective longitudinal study was conducted at Swat Medical College and its affiliated Hospitals from January 2022 to January 2023. A total of 195 pregnant women, deemed high-risk for preeclampsia based on clinical history and initial screening, were recruited for the study. Participants were followed from their first trimester until delivery, allowing for comprehensive monitoring of biochemical variables over time.

The criteria for inclusion were pregnant women aged 18 years and older and women identified as high-risk for preeclampsia, including those with a history of hypertension, diabetes, or previous preeclampsia, as well as those presenting with elevated blood pressure or proteinuria during

pregnancy. The criteria for exclusion include Women with pre-existing medical conditions unrelated to pregnancy that could affect the study outcomes and multiple gestations (e.g., twins, triplets).
At the initial visit (first trimester), demographic data and medical histories were recorded. Blood pressure measurements were taken and blood samples were collected for baseline biochemical analyses. Participants underwent scheduled follow-up visits in the second trimester and third trimester. At each visit, blood pressure was monitored, and additional blood samples were collected to measure biochemical variables of interest.
Using Aseptic venipuncture technique, blood samples were collected from participants at three intervals during pregnancy (first trimester, second trimester, and third trimester). Biochemical markers including Placental Growth Factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), uric acid, creatinine, and serotonin were collected in serum separator tubes following centrifugation and were stored at -80°C until analysis. Strict quality control measures were taken including equipment calibration, adherence to standard operating procedures and ethical approval from the Swat Medical College Ethics Committee.
Statistical analysis was done using SPSS 23. Longitudinal changes in biochemical variables were analyzed using repeated measures ANOVA to assess intra-individual variations over time. Correlation analyses were performed to explore associations between biochemical markers and clinical outcomes, such as the development of preeclampsia.

RESULTS

The alterations in key biochemical markers throughout pregnancy was a steady decline in Placental Growth Factor (PlGF) from the first to the third trimester, signifying a likely decrease in placental function over time. In contrast, there is an increase observed in 'soluble fms-like tyrosine kinase-1 (sFlt-1) which may indicate heightened endothelial dysfunction' as there is progression in pregnancy. There s a gradual increase in levels of uric acid and creatinine which reflects renal stress commonly associated with advancing gestation. Rise in levels of serotonin in increments throughout trimesters suggests a progressive physiological adaptation or potential role in vascular regulation during pregnancy. (Table 1) (Figure 1)The mean values of biochemical markers in women with preeclampsia with those who did not have were compared. All the markers studied showed significant differences. Explicitly, women with preeclampsia showed low PlGF levels and higher sFlt-1 levels compared to non-preeclampsia counterparts which indicates impaired angiogenic balance and increased endothelial dysfunction. Levels of uric acid and creatinine in the preeclampsia group were elevated which suggested heightened renal involvement, a hallmark of severe preeclampsia. Levels of Serotonin levels were also significantly high in women with preeclampsia, associating its role in pathophysiology of hypertensive disorders in pregnancy. (Table 2) (Figure 2)This table presents correlation coefficients between serotonin levels and clinical parameters associated with preeclampsia. High levels of serotonin are associated with increased blood pressure and proteinuria, which are fundamental features of preeclampsia. The negative association with gestational age suggests that the timings and severity of onset of preeclampsia is affected by levels of serotonin. Hence these results highlight the potential role of serotonin as a biomarker or therapeutic target in managing hypertensive disorders of pregnancy, providing understandings into its role in vascular dysfunction and disease progression. (Table 3)(Figure 3)

Table 1: Longitudinal Changes in Biochemical Markers

Biomarker	First Trimester (Mean ± SD)	Second Trimester (Mean ± SD)	Third Trimester (Mean ± SD)
Placental Growth Factor (PlGF)	151 (± 21)	141 (± 19)	121 (± 16)

'Soluble fms-like tyrosine kinase-1' (sFlt-1)	52 (± 9)	61 (± 11)	81 (± 13)
Uric Acid (mg/dL)	4.6 (± 0.6)	5.1 (± 0.8)	5.6 (± 0.9)
'Creatinine' (mg/dL)	0.8 (± 0.3)	0.10 (± 0.3)	1.2 (± 0.4)
Serotonin (ng/mL)	51 (± 6)	56 (± 7)	61 (± 8)

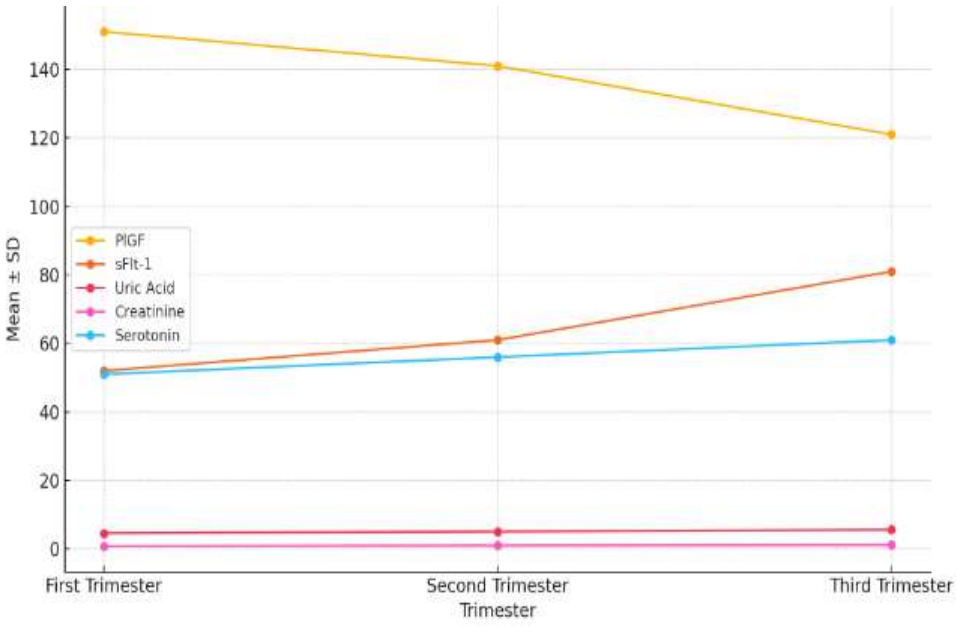
Table 2: Comparison of Biochemical Markers in Preeclampsia vs. Non-Preeclampsia

Biomarker	Preeclampsia (Mean ± SD)	Non-Preeclampsia (Mean ± SD)	p-value
Placental Growth Factor (PlGF)	101 (± 16)	141 (± 19)	0.023
Soluble fms-like tyrosine kinase-1 (sFlt-1)	91 (± 13)	61 (± 11)	0.012
Uric Acid (mg/dL)	6.1 (± 1.0)	5.1 (± 0.8)	0.001
Creatinine (mg/dL)	1.3 (± 0.5)	1.0 (± 0.4)	0.022
Serotonin (ng/mL)	66 (± 9)	56 (± 7)	0.011

Table 3: Correlation Analysis between Serotonin Levels and Clinical Parameters

Clinical Parameter	Correlation Coefficient (r)	p-value
Blood Pressure (mmHg)	0.46	0.023
Proteinuria (g/24h)	0.31	0.013
Gestational Age (weeks)	-0.21	0.054

Figure 1: The graph line shows the mean levels of various biochemical markers throughout three trimesters of pregnancy.



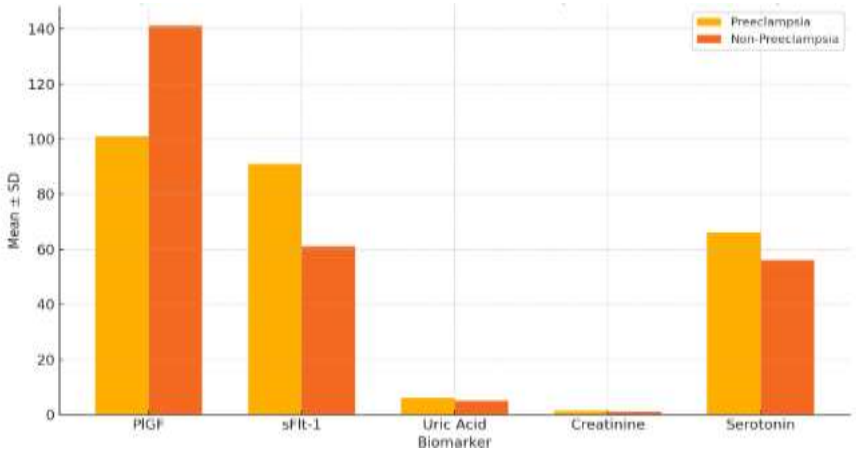


Figure 2: The Bar chart compares the mean levels of biochemical markers between women with preeclampsia and those without.

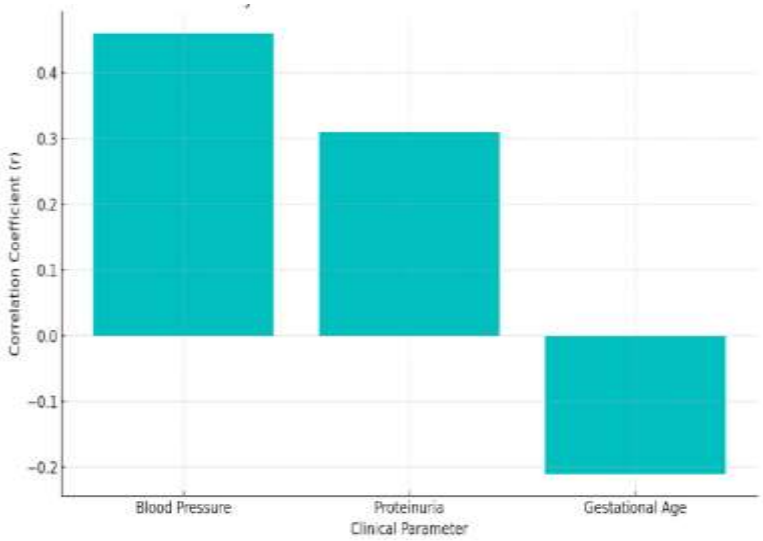


Figure 3: The bar graph shows correlation coefficient between serotonin levels and clinical parameters.

DISCUSSION

Due to its unpredictable onset and potential for causing serious complication in the mother and fetus, preeclampsia poses a significant challenge in obstetrics. The present investigation noted a progressive decrease in PlGf and increase in sFlt-1in women who developed preeclampisa throughout pregnancy. Our results are also in accordance to a study conducted by Zhu X et al., 2020 who observed 'decrease in PlGf and increase in sFlt-1' in preeclampsia patients.[14] In accordance to our findings, a study conducted by Stepan H et al., 2023 showed similar results.[15] In accordance to our findings Rana S et al., 2020 also showed an imbalance in angiogenic factors predisposing to endothelial dysfunction and hypertension characteristic of preeclampsia.[16] Our findings are also in accordance with a study conducted by Santoyo JM et al., 2022.[17] The significant elevation in uric acid and creatinine levels in our preeclampsia participants further correlates with a study conducted by Khaliq OP et al., 2018 who showed an increase in serum uric acid in preeclampsia patients.[18] Our results are also in accordance to a study conducted by Tesfa E et al., 2022 who also observed increase in the levels of uric acid and creatinine in the pregnant patients who had preeclampsia.[19]In the present study high levels of serotonin were observed in women who developed preeclampsia thus showing a potential role of serotonin in preeclampsia pathophysiology possibly through effecting its vascular tone and endothelial function modulation. Our results are in accordance with Gumusoglu S et al., 2021 who

showed increase in serotonin levels in preeclampsia patients.[20] The findings of the study conducted by Serena G et al., 2021 also coincides with our study findings. They also showed increase in levels of serotonin in preeclampsia patients.[21] However, there is limited research on affects of serotonin in pregnancy-related hypertensive disorders, studies on cardiovascular diseases highlights its vasoactive properties and potential implications for pregnancy outcomes.[22]

CONCLUSION

Our study contributes to the understanding of biochemical dynamics specifically highlighting the role of PlGF, sFlt-1, uric acid, creatinine and serotonin in the progression of preeclampsia. Hence these biomarkers are very important in the early diagnosis and treatment of those pregnant women who are at risk of developing preeclampsia thus contributing to the understanding of pathophysiology of the condition along with helping in development of targeted therapeutic strategy.

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