ROLE OF INFLAMMATORY CYTOKINES (IL-6 AND TNF-A) AND C-REACTIVE PROTEIN AS MEDIATORS OF INFLAMMATION IN SEVERE PREECLAMPSIA

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ABSTRACT
This hospital-based observational case-control study evaluated the role of inflammatory cytokines (IL-6 and TNF-α) and C-reactive protein (CRP) as mediators of inflammation in severe preeclampsia. There is growing evidence that inflammatory cytokines in particular, Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α), as well as C-Reactive Protein (CRP) are important in the pathogenesis and progression of severe preeclampsia. To assess the serum levels of IL-6, TNF-α, and CRP in women with severe preeclampsia and compare them with women of similar gestational age without preeclampsia (normotensive pregnant women), the present hospital-based observational case-control study was undertaken. One hundred and ten pregnant women were enrolled, 55 with severe preeclampsia and 55 with normal pregnancies. The inflammatory markers in the serum were estimated by ELISA, and the routine biochemical parameters were also determined. Data were analysed using the Independent Student's t-test for comparison between groups and Pearson's correlation analysis to assess the association between inflammatory markers and clinical as well as biochemical parameters. Women with severe preeclampsia showed much higher serum concentrations of IL-6, TNF-α and CRP than controls ($p<0.001$). The inflammatory markers had significant positive correlations with SBP, DBP, serum creatinine, uric acid and liver enzymes, which suggested their relationship with the level of severity of the disease and organ dysfunction. The results corroborate the key role of inflammation in the development of severe preeclampsia and indicate that the inflammatory markers, namely IL-6, TNF-α and CRP, can be useful to identify the severity of the disease and to monitor the course of preeclampsia. These findings suggest that assessment of IL-6, TNF-α, and CRP may aid in early risk stratification and closer clinical monitoring of women with severe preeclampsia. Further multicentre studies with larger sample sizes are required to confirm these findings and to evaluate their clinical use.
Keywords: Severe preeclampsia, Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), C-Reactive Protein (CRP), Cytokines, Endothelial dysfunction.
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1. INTRODUCTION

Pregnancy is a special physiological condition in which the maternal immune system dramatically changes to provide for growth and development of the fetus, while still keeping the mother safe from infection. A properly-controlled inflammatory response is key to pregnancy and is crucial in the onset of pregnancy, development of the placenta, fetal development, and labour. The inflammatory response is normally balanced, but if it is excessive or uncontrolled it can disrupt maternal and fetal homeostasis. These disruptions are involved in various obstetric complications such as preeclampsia, one of the most important causes of maternal and perinatal morbidity and mortality in the world today. During pregnancy, the maternal immune system becomes tolerant to the semi-allogenic fetus without losing its ability to react to infectious agents.

This adaptation is a complex interaction between immune cells, cytokines and placental tissue. Uterine natural killer cells, macrophages and regulatory T cells have important roles in maintaining immune balance and in a successful placentation. Immune tolerance plays a crucial role in a normal pregnancy by preventing rejection of fetal tissues by the mother. When these adaptive mechanisms fail, the placenta fails to develop properly, contributing to the development of pregnancy-related disorders like preeclampsia. Maternal immune tolerance is regulated by T helper (Th) lymphocytes that secrete a variety of cytokines. A balance of anti-inflammatory Th2 cytokines with pro-inflammatory Th1 cytokines is generally considered to be normal pregnancy. This equilibrium is crucial for immune tolerance and normal placental function. These changes in the cytokine profile, which includes an increase in pro-inflammatory mediators like tumour necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6), may lead to systemic inflammation and endothelial damage.

These immunologic changes are thought to play a significant role in the pathogenesis and progression of preeclampsia. Preeclampsia is a multisystem disease defined by new onset of hypertension and proteinuria after 20 weeks gestation. It is linked to generalized endothelial dysfunction and hyper activation of the inflammatory response in

pregnancy. The immune activation in preeclamptic women results in an increased production of inflammatory cytokines, oxidative stress and vascular damage. These pathological changes lead to diminished placental perfusion and multiple organ dysfunction in the mother like kidney, liver and cardiovascular system. The severity of the inflammatory response correlates with severity of disease and maternal/fetal outcome. Appropriate invasion of trophoblast cells into early pregnancy maternal spiral arteries is necessary for successful placental development. This process transforms the spiral arteries into vessels with low resistance that can provide enough blood to the growing baby. The invasion of the trophoblast and incomplete remodeling of the spiral arteries leads to decreased uteroplacental blood flow in preeclampsia. As a result, placental ischemia and hypoxia occur, leading to a cascade of inflammatory and oxidative pathways that play a major role in the pathogenesis of severe preeclampsia.

Placental ischemia triggers inflammatory cytokines, anti-angiogenic factors and reactive oxygen species to be released into the maternal circulation. These circulating mediators activate endothelial cells, causing generalized endothelial dysfunction, vasoconstriction, increased vascular permeability and coagulation abnormalities. This endothelial damage is responsible for the clinical features of preeclampsia such as hypertension, proteinuria, oedema and dysfunction of various organs. Therefore, endothelial dysfunction is a significant pathobiological process that is a link between placental abnormalities and maternal clinical manifestations. Preeclampsia is a complex condition with inflammatory cytokines playing a pivotal role in its pathophysiology through immune activation, endothelial damage and oxidative stress. A consistent increase in levels of pro-inflammatory mediators has been linked to severity and organ involvement. These cytokines affect the tone of blood vessels, the coagulation system and inflammatory processes, aggravating maternal complications. Therefore, the assessment of inflammatory markers could give important information about the activity and severity of the disease, and could be considered potential biomarkers for diagnosis, prognosis and monitoring of preeclampsia.

Pro-inflammatory cytokines that play a key role in immune regulation include interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). IL-6 stimulates acute phase inflammatory response and synthesis of proteins like C-reactive protein and TNF-α is responsible for endothelial activation, oxidative stress and vascular dysfunction. Many clinical investigations have revealed the presence of increased levels of both IL-6 and TNF-α in the serum of women with severe preeclampsia. These have been linked to disease severity, hypertension, renal impairment, and liver dysfunction. C-Reactive Protein (CRP) is an acute-phase protein, produced by the liver in response to the inflammatory cytokines, specifically IL-6. It is an important indicator of global inflammation and has been extensively applied in clinical practice to monitor inflammatory disorders. Increased CRP has been noted in women with preeclampsia and is thought to be a reflection of the underlying inflammatory state and endothelial dysfunction. CRP levels have also been correlated with greater severity of the disease, suggesting that it may also serve as a biomarker for serious preeclampsia.

Several studies have investigated the role of inflammatory cytokines and CRP in the pathogenesis of preeclampsia. However, their precise relationship with disease severity remains incompletely understood. Moreover, there is still a lack of data on evaluation of IL-6, TNF-α and CRP together with clinical and biochemical parameters in Indian population. The present study was thus undertaken to assess the serum levels of IL-6, TNF-α and CRP in women with severe preeclampsia and their correlation with blood pressure, renal function, liver function and severity of preeclampsia, to gain further insight into their role as markers of inflammation.

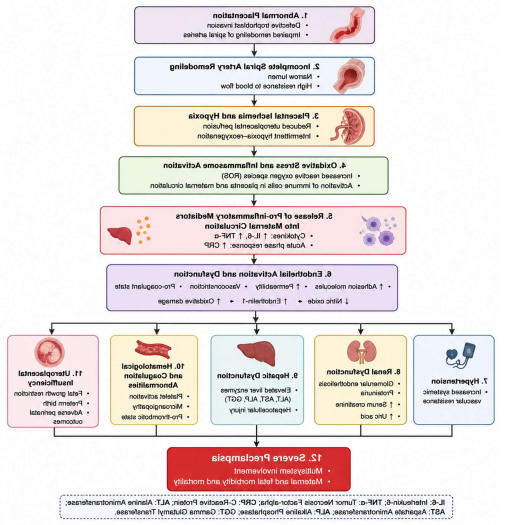

Figure 1: Conceptual Pathogenesis of Severe Preeclampsia Involving Inflammatory Cytokines

2. REVIEW OF LITERATURE

Studies Reporting Elevated Inflammatory Markers

Teran et al. (2001) To investigate the concentration of markers of inflammation in non-pregnant women, women with normal pregnancy and women with pre-eclampsia. Methods: Pregnant women (n=26), women with pre-eclampsia (n=25) and non-pregnant normotensive women (n=21) were included in the study. C-reactive protein was measured by latex-enhanced immunoturbidimetric assay, serum tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-**6)** by high sensitivity ELISA.

Kruskal–Wallis non-parametric analysis of variance followed by the Mann–Whitney U-test were used for statistical analyses. Results: Higher values (mean±S.E.M.) of C-reactive protein were found in pre-eclampsia (4.11±0.37 mg/dl) compared with normal pregnant women (2.49±0.26 mg/dl) and non-pregnant controls (1.33±0.15 mg/dl). TNF-α was significantly higher in women with pre-eclampsia (15.74±5.09 pg/ml), in relation to the control group (2.76±0.41 pg/ml) and women with normal pregnancy (8.31±1.55 pg/ml). IL-6 levels were significantly higher in pre-eclamptic women (12.91±1.29 pg/ml) compared with normal pregnant (5.07±0.423 pg/ml) and control women (1.25±0.13 pg/ml). Conclusions: The results of this cross-sectional study in a high-risk Andean population show that both C-reactive protein and pro-inflammatory cytokines are present in higher concentrations in women with pre-eclampsia. The study was undertaken in women with established pre-eclampsia and it is not possible to determine whether the increased concentrations of C-reactive protein and pro-inflammatory cytokines were a cause or consequence of the disease.

Afshari et al. (2005) Our objective was to determine the role of Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-alpha), markers of immune activation and endothelial dysfunction, in patients with preeclampsia. Twenty four women with preeclampsia and eighteen antepartum normotensive pregnant women were recruited as controls. Serum levels of IL-6 and TNF-alpha were measured by enzyme-linked immunosorbent assay. We used independent-samples t test to assess the differences in the concentration of cytokines in preeclamptic patients and control subjects. IL-6 levels [mean (S.D.)] were significantly higher in preeclamptic women [5.8 (4.85) pg/ml] compared to normal pregnant women [3.01 (2.45) pg/ml] ($p = 0.02$). There was no significant change in concentration of TNF-alpha in preeclamptic women [53.8 (30.0) pg/ml] compared to normal pregnant women [51.9 (33.8) pg/ml] ($p > 0.1$). The results of this study show that IL-6 as a pro-inflammatory cytokine is present in higher concentration in women with preeclampsia. The study was undertaken in women with established preeclampsia and it is not possible to determine whether the increased concentration of IL-6 is a cause or consequence of the disease. Furthermore, these findings suggest that serum TNF-alpha level is not associated with preeclampsia.

Kong et al. (2018) The expression of inflammatory factors, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP), in patients with pregnancy-induced hypertension (PIH) was investigated, to analyze correlation of expression levels of these factors in patients with unfavorable fetal outcome. A total of 100 patients diagnosed with PIH treated in Jining First People's Hospital (Jining, China) from January 2012 to October 2017 were selected as the experimental group, while 100 normal pregnant women during the same period were selected as the control group. Results showed that the levels of IL-6, TNF-α and hs-CRP in patients with PIH were significantly higher than those in normal pregnant women ($p<0.01$). There were significant differences in levels of IL-6, TNF-α and hs-CRP among patients with hypertension in different degrees. The expression levels of IL-6, TNF-α and hs-CRP in PIH patients with favorable pregnancy outcome were lower than those in patients with unfavorable pregnancy outcome ($p<0.05$). Moreover, the expression levels of IL-6, TNF-α and hs-CRP had a linearly positive correlation with systolic blood pressure in PIH patients. Age, height and weight had no significant correlation with unfavorable pregnancy outcome of PIH patients ($p>0.05$). Finally, inflammatory factors (TNF-α, IL-6 and hs-CRP) and blood pressure were obviously and positively correlated with unfavorable pregnancy outcome of PIH patients ($p<0.05$). In conclusion, the expression of inflammatory factors (TNF-α, IL-6 and hs-CRP) in PIH patients are positively correlated with the systolic blood pressure and unfavorable fetal outcome of patients, which can be used as indexes of prognosis evaluation of PIH patients.

Veiga et al. (2022) Preeclampsia is a serious pregnancy complication that affects 5%–10% of the obstetric population. To study inflammatory markers associated with preeclampsia. Searches of articles on the topic published over a 10-year period (2009–2019) were performed in three databases (PubMed, Cochrane, and Embase) using the keywords preeclampsia and inflammatory markers. The PubMed search using 10 years and humans as filters retrieved 124 articles. Using an advanced search strategy, 0 articles were identified in Embase and 10 articles in Cochrane. After screening and eligibility assessment, 13 articles were included in the systematic review and meta-analysis. Meta-analysis and quality assessment of the studies were performed using the Review Manager 5.3 program. For meta-analysis, women with preeclampsia were compared to control women, i.e., pregnancies without arterial hypertension. Leptin levels were significantly higher ($p < 0.0002$) in women with preeclampsia compared to controls. Total cholesterol was also significantly elevated in women with preeclampsia ($p < 0.0001$). There was no significant difference in HDL between groups, but women with preeclampsia had significantly increased LDL ($p < 0.01$). The same was observed for triglycerides, which were significantly increased in women with preeclampsia ($p < 0.04$) compared to controls. Analysis of TNF-alpha, an important inflammatory marker, showed higher levels in women with preeclampsia ($p < 0.03$) compared to

controls. The same was observed for another important inflammatory marker, interleukin 6, which was significantly increased in women with preeclampsia ($p < 0.0002$). There was a significant increase of C-reactive protein in women with preeclampsia ($p < 0.003$) compared to controls. Women with preeclampsia have increased levels of inflammatory markers compared to control women.

Okikiade, et.al (2025) Hypertensive disorders of pregnancy and pregnancy-induced hypertension(PIH) are often erroneously often erroneously used interchangeably and in remote past collectively termed "toxemia of pregnancy". This continues to represent a critical global health concern, contributing significantly to maternal and perinatal morbidity and mortality. According to the American College of Obstetricians and Gynecologists (ACOG), these disorders affect approximately 2–8% of pregnancies worldwide, underscoring their clinical relevance. Despite advancements in prenatal care, hypertensive conditions remain a substantial cause of maternal death across both lowresource and high-income settings. Regional data indicate that hypertensive disorders account for approximately 26% of maternal deaths in Latin America and the Caribbean, while in Africa and Asia, they contribute about 9%. Even in high-income countries, where maternal mortality rates have declined considerably due to improvements in obstetric care, 16% of maternal deaths are still attributed to these conditions. Among the hypertensive disorders of pregnancy, preeclampsia remains the commonest is characterized by new-onset hypertension after 20 weeks of gestation, often accompanied by proteinuria or signs of systemic organ dysfunction and it is associated with adverse outcomes for both mother and fetus. While the precise pathophysiological mechanisms underlying preeclampsia and related hypertensive conditions remain incompletely defined, mounting evidence implicates dysregulated immune and inflammatory responses as central drivers in their development and progression. One of the prevailing hypotheses posits an imbalance between pro-angiogenic factors (such as vascular endothelial growth factor [VEGF] and placental growth factor [PlGF]) and anti-angiogenic factors (notably soluble fms-like tyrosine kinase-1 [sFlt-1] and soluble endoglin), leading to widespread endothelial dysfunction and impaired placental perfusion. This angiogenic imbalance is believed to be influenced or even triggered by an aberrant maternal immune response to fetal antigens.

Bucher, et.al (2026) Severe complications of preeclampsia, particularly cerebral manifestations such as eclampsia, are a major cause of maternal mortality. Prediction of women at high risk as well as the pathways leading to eclampsia remain poorly understood. This thesis aims to evaluate current approaches for predicting severe complications, to elucidate underlying mechanisms of cerebral complications, and to identify potential targets for neuroprotective interventions. Study I, a systematic review and meta-analysis of predictive tests for maternal and perinatal outcomes in hypertensive disorders of pregnancy, revealed significant heterogeneity across the included studies due to differences of population, predictors and outcomes. For maternal outcomes, only the fullPIERS model could be pooled showing moderate performance with high heterogeneity. Meta-analyses of perinatal outcomes were limited by low study quality. These findings highlight the need for future studies to use standardized definitions and robust external validation of promising predictors. Using a translational approach in studies II and III, we identified elevated levels of blood-brain barrier injury, neuroinflammatory and neurodegenerative markers in the cerebrospinal fluid of women with eclampsia and preeclampsia. These findings indicate significant cerebral involvement comparable to that observed in other severe neurological conditions such as traumatic brain injury. Consistent with these findings, the preeclampsia-like RUPP rat model demonstrated increased blood–brain barrier disruption and endothelial dysfunction. These alterations were associated with astrocyte reactivity and impaired glutamate homeostasis, which may contribute to region-specific changes in neuronal transmission as observed in the rat model. Although apoptotic pathways were upregulated in the cortex, no histological evidence of tissue scaring process was observed. Together, these findings provide novel insights into cerebral involvement in preeclampsia, even in the absence of overt neurological symptoms such as eclamptic seizures. This improved understanding may contribute to the identification of novel therapeutic targets and the development of more accurate predictors for eclampsia.

Mechanistic and Pathophysiological Reviews

Raghupathy et al. (2013) Preeclampsia (PE) is an important, common, and dangerous complication of pregnancy; it causes maternal and perinatal illness and is responsible for a high proportion of maternal and infant deaths. PE is associated with increased blood pressure and proteinuria, with a whole host of other potentially serious complications in the mother and fetus. The maternal syndrome in PE is primarily that of generalized dysfunction of the maternal endothelium, and this generalized endothelial dysfunction appears to be part of an exaggerated systemic inflammatory response that involves maternal leukocytes and proinflammatory cytokines. This review examines evidence that points to a significant role for the maternal immune system; inadequate trophoblast invasion of spiral arteries initiates ischemia and hypoxia in the placenta, resulting in an increased release of

proinflammatory cytokines in the placenta. Placental ischemia and hypoxia also cause the enhanced release of trophoblast microparticles into the maternal circulation which stimulates increased induction of proinflammatory cytokines and the activation of maternal endothelial cells. This activation results in a systemic, diffuse endothelial cell dysfunction which is the fundamental pathophysiological feature of this syndrome. Recent evidence also supports important roles for proinflammatory cytokines in hypertension, proteinuria, and edema which are characteristic features of PE.

Bellos et al. (2018) Preeclampsia is a multi-system hypertensive disorder of pregnancy, with significant rates of maternal and neonatal morbidity. It represents a major cause of preterm birth, as definitive treatment demands fetal delivery. Although its pathophysiology is complicated, placental hypoxia and endothelial dysfunction constitute established pathogenetic steps of the disease. Inflammation is considered to be a crucial mediator of preeclampsia process, as an imbalance between T_H1, T_H2, and T_H17 immune responses is observed. The present review accumulates current knowledge about the contribution of interleukins in preeclampsia, summarizing the pathways through which each interleukin exerts its function in the disease. Also, the role of genetic polymorphisms is explored and the predictive efficacy of maternal serum interleukin levels is evaluated. Finally, recommendations about the safe interpretation of the outcomes, as well as guidance for future research, are provided.

Predictive Value of Biomarkers

Oancea et al. (2014) A low degree of infl ammation has been associated with complications in pregnancies, including preeclampsia (PE). The aim of our study was to determine the serum values of high sensitivity C Reactive Protein (hs-CRP) and Interleukin-6 (IL-6) in the fi rst and second trimesters of pregnancy in pregnant women with risk factors for the development of PE, and to evaluate their relevance for the prediction of this disorder. Material and methods: We performed a prospective longitudinal study on 120 pregnant women, who were divided based on the pregnancy evolution, into two groups: group I – 26 pregnant women who developed preeclampsia and group II – 94 pregnant women with physiological evolution of pregnancy. Results: Our study has shown an increase in serum levels of hs-CRP and IL-6 in the fi rst and second trimester of pregnancy in patients from group I, signifi cant values being revealed only in the second trimester of pregnancy. The predictive power of the selected infl ammatory markers was signifi cant only for values of hs-CRP in the second trimester of pregnancy, while the association with IL-6 increased the prediction. Conclusions: Increased values of hs-CRP and IL-6 in the second trimester of pregnancy are associated with higher risk for preeclampsia, however the study provided only a modest effi ciency of the prediction capacity

Conflicting Evidence

Serrano et al. (2020) Multiple small studies have suggested that women with pre-eclampsia present elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6). However, little is known regarding the source of this CRP and IL-6 increase. Therefore, the aim of this study was to evaluate the relationship between CRP and IL-6 levels with pre-eclampsia considering different confounding factors. Using data from a large Colombian case-control study (3,590 cases of pre-eclampsia and 4,564 normotensive controls), CRP and IL-6 levels were measured in 914 cases and 1297 controls. The association between maternal serum levels of CRP and IL-6 with pre-eclampsia risk was evaluated using adjusted logistic regression models. Pre-eclampsia was defined as presence of blood pressure ≥140/90 mmHg and proteinuria ≥300mg/24 h (or ≥1 + dipstick). There was no evidence of association between high levels of CRP and IL-6 with pre-eclampsia after adjusting for the following factors: maternal and gestational age, ethnicity, place and year of recruitment, multiple-pregnancy, socio-economic position, smoking, and presence of infections during pregnancy. The adjusted OR for 1SD increase in log-CRP and log-IL-6 was 0.96 (95%CI 0.85, 1.08) and 1.09 (95%CI 0.97, 1.22), respectively. Although previous reports have suggested an association between high CRP and IL-6 levels with pre-eclampsia, sample size may lack the sufficient power to draw robust conclusions, and this association is likely to be explained by unaccounted biases. Our results, the largest case-control study reported up to date, demonstrate that there is not a causal association between elevated levels of CRP and IL-6 and the presence of pre-eclampsia.

Research Gap

Although several studies have examined the involvement of inflammatory cytokines and CRP in preeclampsia, the available evidence remains inconclusive about their exact contribution to the pathogenesis and severity of preeclampsia. Different results have been found in the past about the relationship between inflammatory markers, such as IL-6, TNF-α and CRP, and severe preeclampsia, and few studies have investigated all three inflammatory markers in association with clinical and biochemical markers of endothelial dysfunction and organ damage. In addition, the data on the Indian population are relatively limited, especially in severe preeclampsia. Thus, there is a need to conduct a comprehensive study to evaluate the levels of IL-6, TNF-α and CRP and their correlation with the severity of the disease and other clinical outcomes to help elucidate their potential as markers of inflammation in severe preeclampsia.

3. AIMS AND OBJECTIVES

AIMS: The present study aims to evaluate the role of inflammatory cytokines Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and C-reactive protein (CRP) as mediators of inflammation in severe preeclampsia. The study also seeks to determine their association with disease severity, endothelial dysfunction, and organ damage in affected pregnant women.

OBJECTIVES

1. To determine the serum levels of inflammatory cytokines IL-6 and TNF-α in pregnant women with severe preeclampsia and compare them with normotensive pregnant women.
2. To evaluate the levels of C-reactive protein (CRP) as an inflammatory marker in women with severe preeclampsia.
3. To assess the relationship between inflammatory markers and clinical parameters such as blood pressure, liver enzymes, and renal function tests in preeclamptic women.
4. To investigate the role of inflammatory cytokines and CRP in the pathogenesis and organ damage associated with severe preeclampsia.

4. MATERIALS AND METHODS

Study Design

The present study was designed as a hospital-based observational case-control study to evaluate the levels of inflammatory cytokines (IL-6 and TNF-α) and C-reactive protein (CRP) in women with severe preeclampsia and compare them with gestational age-matched normotensive pregnant women.

Study Setting

The study was carried out in the Department of Obstetrics and Gynecology in collaboration with the Department of Biochemistry at a tertiary care teaching hospital in Eastern Uttar Pradesh, India. The study was conducted after obtaining approval from the Institutional Ethics Committee.

Duration of Study

The study was conducted during the period of July 2025 to June 2026.

Study Population

The study population consisted of pregnant women attending the antenatal outpatient and inpatient departments of the Department of Obstetrics and Gynecology. Eligible participants included women with severe preeclampsia and healthy normotensive pregnant women.

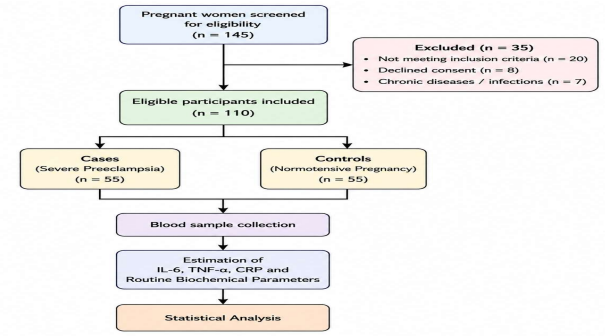

Figure 2. Flow Chart of Participant Recruitment

Sample Size

A total of 110 pregnant women were included in the study, comprising 55 women with severe preeclampsia (cases) and 55 gestational age-matched normotensive pregnant women (controls). The sample size was calculated using the formula for comparison of two independent means:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

where:

- n = sample size required in each group
- $Z_{\alpha/2}$= standard normal deviate at 95% confidence level (1.96)
- Z_{β}= standard normal deviate corresponding to 80% study power (0.84)
- $\sigma_1$and σ_2= standard deviations of the two groups
- $\mu_1 - \mu_2$= expected difference in mean biomarker levels between the groups

Study Groups

Group I (Cases)

- 55 pregnant women diagnosed with severe preeclampsia.

Group II (Controls)

- 55 healthy normotensive pregnant women matched for gestational age.

Case Definition

Cases included pregnant women diagnosed with severe preeclampsia after 20 weeks of gestation, with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, associated with proteinuria or evidence of maternal organ dysfunction.

Control Definition

Controls included healthy pregnant women with normal blood pressure, matched for gestational age, and without proteinuria or any hypertensive disorder of pregnancy.

Inclusion Criteria

- Pregnant women aged 18–40 years.
- Gestational age of 20 weeks or more.
- Women diagnosed with severe preeclampsia.
- Healthy normotensive pregnant women.
- Singleton pregnancy.

- Willingness to provide written informed consent.

Exclusion Criteria

- Chronic hypertension.
- Diabetes mellitus.
- Chronic renal disease.
- Chronic liver disease.
- Autoimmune disorders.
- Multiple pregnancy.
- Acute or chronic infections.
- Women receiving immunosuppressive therapy.
- Refusal to provide informed consent.

Data Collection Procedure

After obtaining written informed consent, demographic and clinical details were recorded using a structured proforma. Maternal age, gestational age, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were documented. Approximately 5 mL of venous blood was collected under aseptic conditions from each participant. Blood samples were centrifuged, and the separated serum was stored at −80°C until laboratory analysis.

Statistical Analysis

The collected data were entered into Microsoft Excel and analysed using SPSS version 26.0. Continuous variables were expressed as Mean ± Standard Deviation (SD), while categorical variables were expressed as frequencies and percentages. Comparisons between the two groups were performed using the Independent Student's t-test, and Pearson's correlation analysis was used to determine the association between inflammatory markers and clinical as well as biochemical parameters. A p-value <0.05 was considered statistically significant.

Laboratory Investigations (IL-6, TNF-α, CRP, and Routine Biochemical Parameters)

Serum levels of Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and C-Reactive Protein (CRP) were estimated using commercially available ELISA kits according to the manufacturer's instructions. The assay detection range, analytical sensitivity, and intra-/inter-assay coefficients of variation were as specified by the manufacturer.

Routine biochemical investigations included:

- Serum Creatinine
- Blood Urea
- Serum Uric Acid
- Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Alkaline Phosphatase (ALP)
- Gamma-Glutamyl Transferase (GGT)

Blood pressure (SBP and DBP), gestational age, and body mass index (BMI) were also recorded for all participants.

Correlation of IL-6 and TNF-α with Clinical and Biochemical Parameters

The relationship of IL-6, TNF-α, and CRP with systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, uric acid, AST, ALT, ALP, and GGT was evaluated using Pearson's correlation analysis. The correlation findings are presented in the Results.

5. RESULTS

In the present study 110 pregnant women were included, 55 who had severe preeclampsia (cases) and 55 gestational age-matched normotensive pregnant women (controls). The clinical and laboratory features of the study subjects are shown in Table 5.1. In women with severe preeclampsia, the mean values of the most important parameters were significantly higher: SBP, DBP, BMI, serum creatinine, uric acid, urea, liver enzymes (ALT, AST, ALP, GGT), inflammatory markers (IL-6, CRP, TNF-α). There were no significant differences in gestational age or in maternal age between the two groups.

Table 1. Clinical and Laboratory Characteristics of the Study Participants

Characteristics	Severe Preeclampsia (N = 55) Mean ± SD	Controls (N = 55) Mean ± SD	Mean Difference	P value
Age (years)	30.84 ± 5.72	30.29 ± 5.41	0.55	0.61
SBP (mmHg)	168.42 ± 19.83	111.35 ± 11.94	57.07	<0.001*
DBP (mmHg)	108.74 ± 11.56	71.26 ± 6.12	37.48	<0.001*
Gestational Age (weeks)	31.18 ± 3.64	31.71 ± 3.98	−0.53	0.48
BMI (kg/m²)	30.26 ± 4.18	27.43 ± 3.91	2.83	0.012*
Creatinine (µmol/L)	109.62 ± 28.34	67.18 ± 13.45	42.44	<0.001*
Uric Acid (µmol/L)	418.74 ± 82.63	232.19 ± 46.71	186.55	<0.001*
Urea (mmol/L)	5.42 ± 1.83	3.91 ± 0.94	1.51	<0.001*
ALT (U/L)	36.48 ± 14.71	20.12 ± 6.43	16.36	<0.001*

AST (U/L)	49.83 ± 18.22	23.17 ± 5.74	26.66	<0.001*
ALP (U/L)	236.52 ± 61.84	167.39 ± 39.58	69.13	<0.001*
GGT (U/L)	34.71 ± 13.45	17.64 ± 5.29	17.07	<0.001*
IL-6 (pg/mL)	78.34 ± 28.71	16.93 ± 7.82	61.41	<0.001*
CRP (mg/L)	32.56 ± 11.84	6.84 ± 3.19	25.72	<0.001*
TNF-α (pg/mL)	38.74 ± 15.63	12.26 ± 5.42	26.48	<0.001*

Values are expressed as Mean ± SD. Comparisons were performed using the Independent Student's t-test. Corresponding 95% confidence intervals for the mean differences are available from the statistical analysis (SPSS output). Statistical significance was considered at $p < 0.05$.

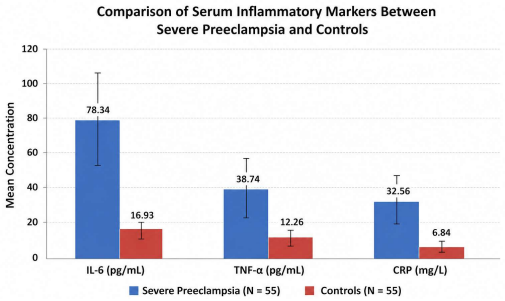

Figure 3: Comparison of Serum IL-6, TNF-α, and CRP Levels in Severe Preeclampsia and Controls

Table 5.2 shows the correlation between inflammatory markers and selected clinical and biochemical parameters of women with severe preeclampsia. When IL-6 was correlated with other markers, it showed significant positive correlations with SBP, DBP, serum creatinine, uric acid, liver enzymes (AST, ALT, ALP, and GGT) which suggested that elevations in IL-6 levels were linked to greater disease severity. Likewise, there were significant positive correlations of the TNF-α with all the clinical and biochemical parameters assessed. CRP was also found to be highly positively correlated with blood pressure and renal function indices, along with liver enzymes, indicating its association with endothelial dysfunction and involvement of organs in severe preeclampsia.

Table 2. Correlation of Inflammatory Markers with Clinical and Biochemical Parameters in Severe Preeclampsia

Parameters	IL-6 (r)	TNF-α (r)	CRP (r)
SBP	0.581*	0.534*	0.517*
DBP	0.542*	0.501*	0.496*
Creatinine	0.447*	0.418*	0.392*
Uric Acid	0.473*	0.451*	0.428*
AST	0.416*	0.387*	0.365*
ALT	0.351*	0.326*	0.301*
ALP	0.438*	0.405*	0.471*
GGT	0.297*	0.284*	0.269*

*r = Pearson's correlation coefficient. Statistically significant at $p < 0.05$.

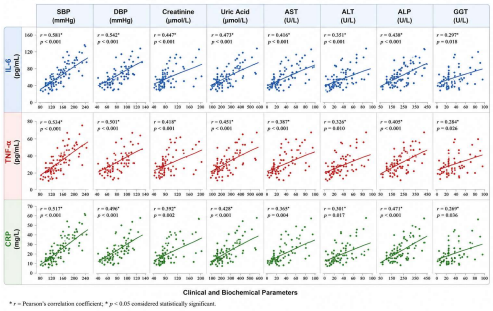

Figure 4: Correlation of Inflammatory Markers with Clinical and Biochemical Parameters in Severe Preeclampsia

6. DISCUSSION

The aim of the present study was to assess the levels of inflammatory cytokines (IL-6 and TNF-α) and C-reactive protein (CRP) in severe preeclampsia and to compare them with gestational age matched normotensive pregnant women. The results showed that women with severe preeclampsia had significantly higher levels of IL-6, TNF-α and CRP, highlighting an exaggerated inflammatory response in women with preeclampsia. These inflammatory markers were also positively correlated with the parameters of renal function and liver enzymes, indicating the relationship of these markers with hypertension and organ dysfunction. These observations reinforce the idea that inflammatory cytokines play a role in endothelial damage and disease in severe preeclampsia.

The findings of the present study are consistent with those reported by Raghupathy et al. (2013), who described preeclampsia as an exaggerated systemic inflammatory state characterized by increased production of pro-inflammatory cytokines and generalized endothelial dysfunction. Similarly, significantly elevated serum IL-6, TNF-α, and CRP levels observed in the present study support the role of inflammation in disease progression. The present findings also agree with the systematic review and meta-analysis by Veiga et al. (2022), which demonstrated significantly higher circulating levels of IL-6, TNF-α, and CRP in women with preeclampsia than in normotensive pregnant women. Likewise, Bellos et al. (2018) emphasized the central role of interleukins in immune dysregulation, placental inflammation, and endothelial dysfunction during preeclampsia, supporting the elevated IL-6 levels observed in the present study. The observations are further supported by Okikiade et al. (2025), who

highlighted dysregulated cytokine- and chemokine-mediated inflammatory pathways as key contributors to endothelial dysfunction and the development of pregnancy-induced hypertension, reinforcing the importance of inflammatory mediators in hypertensive disorders of pregnancy. Furthermore, Bucher (2026) demonstrated that severe preeclampsia is associated with neuroinflammation, blood–brain barrier injury, and endothelial dysfunction, indicating that inflammatory mechanisms extend beyond placental pathology to involve systemic and cerebral complications. Although the present study did not evaluate neurological biomarkers, the significantly elevated inflammatory markers observed may reflect the widespread inflammatory processes described by Bucher. However, Serrano et al. (2020) reported no significant independent association between IL-6 and CRP levels and preeclampsia after adjustment for multiple confounding factors. This discrepancy may be explained by differences in study design, sample size, disease severity, population characteristics, timing of sample collection, laboratory methods, and adjustment for confounding variables. Unlike the large multicenter study by Serrano et al., the present study specifically included women with severe preeclampsia, in whom inflammatory activation is expected to be more pronounced.

This study is strengthened by having a gestational age matched control group and the simultaneous assessment of several inflammatory markers in addition to normal biochemical parameters. The generalizability of the findings may be limited, however, due to the relatively small number of participants and centre design. Increased cytokine levels overall suggest the key pathophysiological role of inflammation in severe preeclampsia, and that serum IL-6, TNF-α and CRP are potential disease markers of disease severity and clinical course.

Strengths and Limitations

The present study has several strengths. It employed a hospital-based case-control design with gestational age-matched controls, reducing potential confounding due to differences in pregnancy duration. Simultaneous assessment of IL-6, TNF-α, and CRP together with routine biochemical parameters enabled a comprehensive evaluation of inflammatory status and organ dysfunction in severe preeclampsia. Standardized laboratory methods and uniform statistical analyses further enhanced the reliability of the findings.

However, certain limitations should be acknowledged. The study was conducted at a single tertiary care center with a relatively modest sample size, which may limit the generalizability of the findings. The cross-sectional design does not permit establishment of causal relationships between inflammatory markers and disease progression. In addition, serial measurements of cytokines during pregnancy and assessment of maternal and neonatal outcomes were not performed. Future multicenter prospective studies with larger populations and longitudinal follow-up are recommended to validate these findings and determine the prognostic utility of inflammatory biomarkers in severe preeclampsia.

7. CONCLUSION

In the present study, the serum levels of Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α) and C-Reactive Protein (CRP) were significantly higher in women developing severe preeclampsia than in the normotensive pregnant women of similar gestational age. These inflammatory markers were found to be positively correlated with blood pressure, renal function parameters and liver enzymes which suggests their relationship with the severity of the disease and the organ dysfunction. The results confirm the involvement of inflammation in the pathogenesis of severe preeclampsia and propose that IL-6, TNF-α and CRP could be suitable biomarkers for the evaluation of severe preeclampsia and for monitoring disease course. Future multicenter studies involving larger populations are warranted to validate these findings and establish the clinical utility of these biomarkers in the early diagnosis and prognosis of severe preeclampsia.

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