

Association of Triple Marker and Oxidative Stress Biomarker in the Pathophysiology of Pre-Eclampsia

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ABSTRACT

Pre-eclampsia is a major hypertensive disorder of pregnancy associated with significant maternal and perinatal morbidity and mortality. Oxidative stress, placental hormonal dysregulation, and inflammatory–biochemical disturbances are increasingly recognized as key contributors to its pathophysiology.

Materials and Methods: This hospital-based cross-sectional study included 200 pregnant women, comprising 100 pre-eclamptic cases and 100 gestational age–matched normotensive controls. Pre-eclampsia was diagnosed according to ACOG criteria. Oxidative stress markers, pregnancy-related hormones, and inflammatory parameters were measured in venous blood samples. Statistical analysis was performed using the Independent Student's t-test.

Results: Women with pre-eclampsia showed significantly elevated oxidative stress markers, including catalase, superoxide dismutase, nitric oxide, and malondialdehyde, along with reduced glutathione levels. Estriol, β -human chorionic gonadotropin, and alpha-fetoprotein levels were significantly increased, indicating placental endocrine dysfunction. Serum ferritin and uric acid levels were also markedly higher, reflecting enhanced inflammation and metabolic stress ($p < 0.001$).

Conclusion: The findings demonstrate that pre-eclampsia is characterized by pronounced oxidative stress, hormonal imbalance, and increase inflammatory cascade, highlighting the role of placental dysfunction and endothelial injury in disease progression.

Keywords: Pre-eclampsia, Oxidative stress, Inflammatory biomarkers, Endothelial dysfunction.

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INTRODUCTION

Hypertensive disorders of pregnancy (HDP) remain a leading cause of maternal and perinatal morbidity and mortality worldwide, affecting approximately 7%–12% of pregnancies and accounting for nearly 14% of global maternal deaths [1]. Among these, pre-eclampsia (PE) is the most clinically significant subtype, complicating 3%–5% of pregnancies and contributing substantially to maternal and fetal mortality [2,3]. Gestational hypertension and pre-eclampsia together account for a major proportion of adverse obstetric outcomes, with nearly 10%–20% of women with gestational hypertension progressing to pre-eclampsia [4].

Clinically, pre-eclampsia is defined by the new onset of hypertension after 20 weeks of gestation, with or without proteinuria or evidence of maternal organ dysfunction [5].

It is a pregnancy-specific multisystem disorder involving the cardiovascular, renal, hepatic, neurological, and haematological systems, and its clinical course is often unpredictable [6,7]. Consequently, current guidelines discourage classification into “mild” and “severe” forms, recognizing the potential for rapid progression to life-threatening complications [8].

The placenta plays a central role in the pathogenesis of pre-eclampsia. Normal placentation requires tightly regulated trophoblast proliferation, differentiation, invasion, and spiral artery remodelling to establish an adequate low-resistance uteroplacental circulation [9,10]. In pre-eclampsia, abnormal trophoblast invasion and incomplete spiral artery remodelling result in placental hypoperfusion and chronic hypoxia [11,12]. These placental abnormalities precede maternal clinical

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manifestations and trigger the release of placental-derived factors into the maternal circulation, leading to widespread endothelial dysfunction.

Pre-eclampsia is widely regarded as a multifactorial disorder with a complex and incompletely understood etiology [13]. Current concepts suggest that the disease may arise from primary placental pathology, leading to early-onset pre-eclampsia, or from maternal metabolic and cardiovascular maladaptation, resulting in late-onset disease [14,15]. Although both subtypes share common clinical features, they differ in placental pathology, biochemical characteristics, and prognosis [16–18].

Oxidative stress is a key mechanistic link between placental dysfunction and maternal endothelial injury in pre-eclampsia. While normal pregnancy is associated with increased oxidative activity due to heightened metabolic demands, this is usually counterbalanced by adaptive antioxidant mechanisms [19,20]. In pre-eclampsia, defective placental perfusion and recurrent hypoxia–reperfusion episodes lead to excessive generation of reactive oxygen species, overwhelming antioxidant defences and resulting in enhanced lipid peroxidation, antioxidant depletion, and cellular injury [21]. Maternal endothelial dysfunction, the hallmark of pre-eclampsia, is closely related to oxidative stress–mediated impairment of nitric oxide signaling and vascular homeostasis [21,22].

In addition to its vascular and transport roles, the placenta functions as a major endocrine organ regulating maternal–fetal physiology [10]. Placental dysfunction in pre-eclampsia is therefore accompanied by altered secretion of pregnancy-related hormones, including estriol, β -human chorionic gonadotropin, and alpha-fetoprotein [23–27]. Abnormal levels of these hormones reflect trophoblastic stress, placental hypoxia, and impaired placental permeability, and have been associated with adverse maternal and fetal outcomes.

Oxidative stress in pre-eclampsia is closely intertwined with inflammation. Excess reactive oxygen species activate inflammatory pathways, promoting increased production of pro-inflammatory cytokines and leukocyte activation, while anti-inflammatory mechanisms are relatively suppressed [16,21]. This inflammatory milieu further amplifies endothelial injury and contributes to the clinical manifestations of the disease. Accordingly, inflammatory indices and biochemical markers such as ferritin and uric acid have gained attention as indicators of systemic inflammation, oxidative stress, and metabolic disturbance in pre-eclampsia [28,29].

Elevated maternal serum alpha-fetoprotein (AFP) in pre-eclampsia is associated with increased placental permeability and trophoblastic damage, indicating

impaired placental integrity.[30] Increased β -human chorionic gonadotropin (β -hCG) levels reflect trophoblastic stress and hypoxia-induced hormonal dysregulation.[26] Altered estriol concentrations suggest disturbed placental steroidogenesis and reduced functional capacity of the fetoplacental unit.[10]

Serum ferritin levels are frequently elevated in pre-eclampsia, reflecting systemic inflammation and enhanced oxidative stress.[31] Increased uric acid levels result from impaired renal clearance and placental ischemia and contribute to endothelial dysfunction and inflammatory activation.[22] Nitric oxide bioavailability is altered in pre-eclampsia due to oxidative stress–mediated endothelial dysfunction, leading to reduced vasodilation and increased vascular resistance.[32] Reduced glutathione levels indicate depletion of antioxidant defences, promoting lipid peroxidation and cellular injury.[33] Collectively, disturbances in hormonal, oxidative, and inflammatory markers highlight the multifactorial nature of pre-eclampsia and their contribution to disease progression.[12]

Taken together, the interplay between oxidative stress, placental hormonal dysregulation, and inflammatory–biochemical alterations represents a central mechanism in the pathophysiology of pre-eclampsia. Evaluating these markers in combination may provide a more comprehensive understanding of disease mechanisms and support improved risk stratification and monitoring of affected pregnancies.

MATERIALS AND METHODS

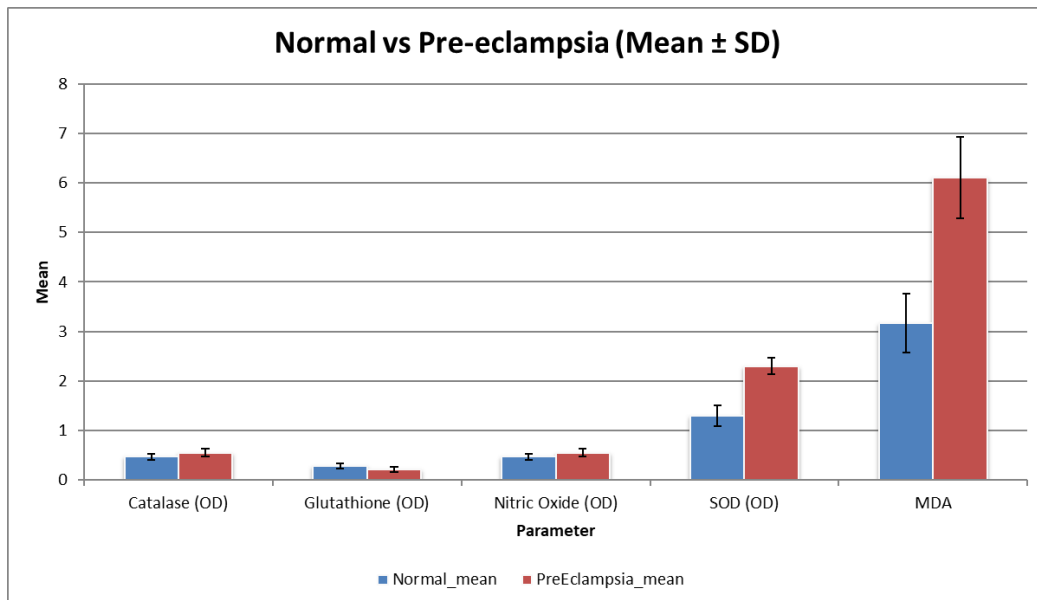
A hospital-based cross-sectional study was conducted at a tertiary health care centre, Thrissur, Kerala, over one and a half years after Institutional Ethics Committee approval. The study included 200 pregnant women, comprising 100 women with pre-eclampsia and 100 gestational age–matched normotensive controls. Pre-eclampsia was diagnosed in women aged <35 years according to ACOG criteria, based on blood pressure $\geq 140/90$ mm Hg with proteinuria (24-hour urine protein ≥ 300 mg, spot urine protein/creatinine ratio ≥ 0.3 , or dipstick $\geq 2+$). Women with chronic hypertension, previous pre-eclampsia/eclampsia, or renal disease were excluded.

After informed consent, Venous blood samples were collected for assessment of oxidative stress markers (catalase, SOD, nitric oxide, glutathione, MDA), hormonal parameters (estriol, β -hCG, alpha-fetoprotein), and biochemical markers (serum ferritin and uric acid). Data were analysed using SPSS version 20, expressed as mean \pm SD, and compared using the Independent Student's *t*-test, with $p < 0.05$ considered statistically significant.

RESULTS

Table 1: Comparison of oxidative stress parameters between normal pregnancy and pre-eclampsia (Independent t-test)

Parameter	Group	Mean ± SD	Std. Error	p-value
Catalase (OD)	Normal	0.47 ± 0.06	0.006	<0.001
	Pre-eclampsia	0.55 ± 0.08	0.008	
Glutathione (OD)	Normal	0.28 ± 0.06	0.006	<0.001
	Pre-eclampsia	0.21 ± 0.06	0.006	
Nitric Oxide (OD)	Normal	0.47 ± 0.06	0.006	<0.001
	Pre-eclampsia	0.55 ± 0.08	0.008	
SOD (OD)	Normal	1.30 ± 0.21	0.02	<0.001
	Pre-eclampsia	2.30 ± 0.17	0.02	
MDA	Normal	3.17 ± .598	.060	<0.001
	Pre-eclampsia	6.10 ± .821	.082	



Graph 1: Comparison of oxidative stress parameters between normal pregnancy and pre-eclampsia (Independent t-test)

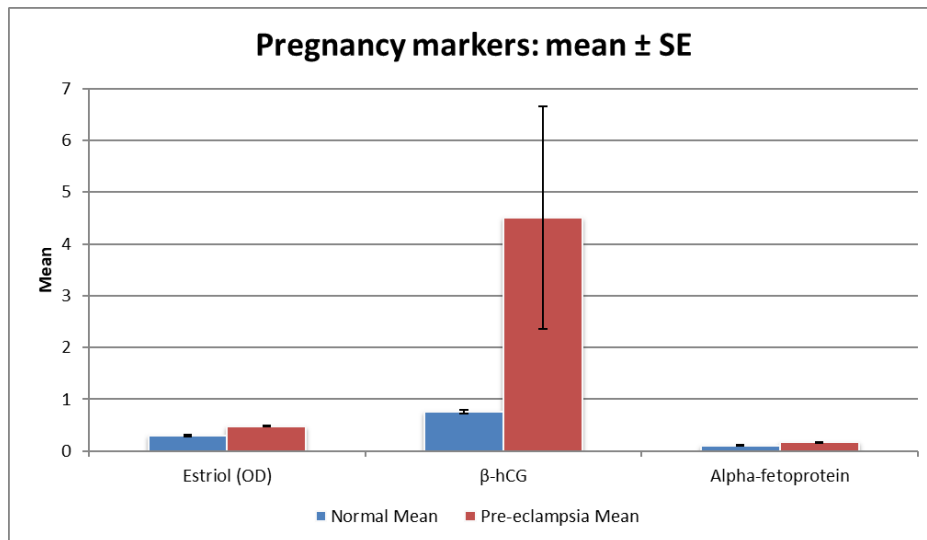
There was a statistically significant difference ($p < 0.001$) in all oxidative stress parameters between normal pregnancy and pre-eclampsia. Women with pre-eclampsia showed significantly elevated levels of catalase, nitric oxide, superoxide dismutase (SOD), and malondialdehyde (MDA) compared to normal pregnant women, while glutathione levels were significantly reduced. The marked increase in MDA levels in pre-eclampsia indicates enhanced lipid peroxidation and severe oxidative stress,

reflecting increased cellular membrane damage. The altered antioxidant profile, characterized by raised catalase and SOD with depleted glutathione, suggests a compensatory but insufficient antioxidant response to excessive reactive oxygen species. Overall, these findings confirm the presence of oxidative stress and impaired redox balance in pre-eclampsia, contributing to its pathophysiology.

Table 2: Mean differences in hormonal and pregnancy-related parameters between normal pregnancy and pre-eclampsia (Independent t-test)

Parameter	Group	Mean ± SD	Std. Error	p-value
Estriol (OD)	Normal	0.30 ± 0.24	0.02	<0.001
	Pre-eclampsia	0.48 ± 0.08	0.01	
β-hCG	Normal	0.76 ± 0.36	0.04	<0.001
	Pre-eclampsia	4.51 ± 21.50	2.15	
Alpha-fetoprotein	Normal	0.11 ± 0.03	0.003	<0.001
	Pre-eclampsia	0.17 ± 0.04	0.004	

Graph 2: Mean differences in hormonal and pregnancy-related parameters between normal pregnancy and pre-eclampsia (Independent t-test)



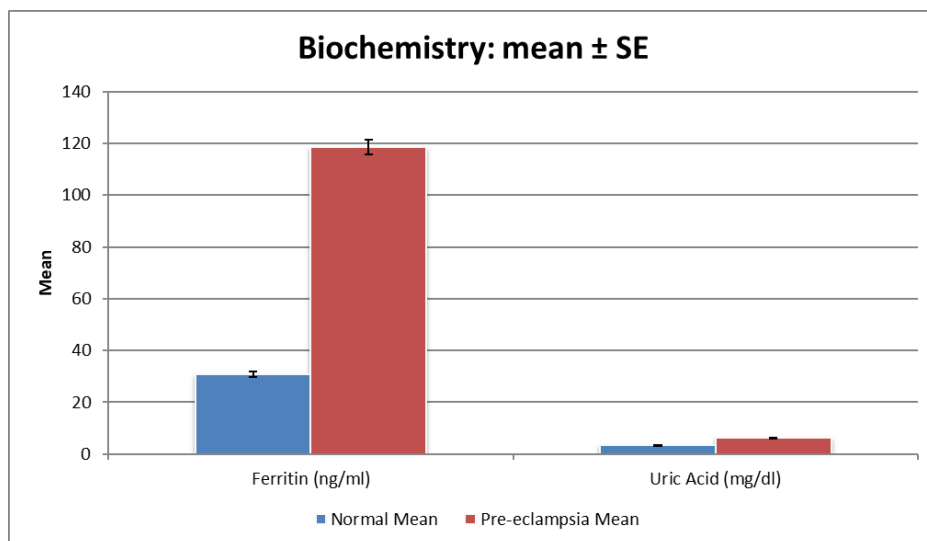
Estriol, β-human chorionic gonadotropin (β-hCG), and alpha-fetoprotein levels were significantly higher in women with pre-eclampsia compared to normal pregnant women ($p < 0.001$). The elevated estriol levels suggest altered placental steroidogenesis, while the marked increase in β-hCG reflects placental hypoxia and trophoblastic stress commonly seen in pre-eclampsia. The

significant rise in alpha-fetoprotein further indicates placental dysfunction and increased placental permeability. Overall, these hormonal alterations point toward disturbed placental function and impaired maternal–fetal hormonal regulation, which play a crucial role in the pathophysiology of pre-eclampsia.

Table 3: Mean differences in general biochemical parameters between normal pregnancy and pre-eclampsia (Independent t-test)

Parameter	Group	Mean ± SD	Std. Error	p-value
Ferritin (ng/ml)	Normal	30.80 ± 11.94	1.19	<0.001
	Pre-eclampsia	118.51 ± 28.70	2.87	
Uric Acid (mg/dl)	Normal	3.54 ± 0.48	0.05	<0.001
	Pre-eclampsia	6.28 ± 0.46	0.05	

Graph 3: Mean differences in general biochemical parameters between normal pregnancy and pre-eclampsia (Independent t-test)



Serum ferritin and uric acid levels were significantly elevated in women with pre-eclampsia compared to those with normal pregnancy ($p < 0.001$). The marked rise in

ferritin reflects an enhanced inflammatory response and increased oxidative stress, as ferritin functions as an acute-phase reactant. The significant elevation of uric acid

suggests impaired renal function, increased cellular turnover, and heightened oxidative stress, all of which are characteristic features of pre-eclampsia. These findings indicate that biochemical and metabolic disturbances, in association with inflammation and oxidative stress, play an important role in the pathogenesis of pre-eclampsia.

DISCUSSION

In our study, women with pre-eclampsia exhibited significant alterations in oxidative stress parameters when compared to normotensive pregnant women, confirming the presence of an exaggerated oxidative stress state (Table 1 & Graph 1). Significantly elevated levels of catalase, superoxide dismutase (SOD), nitric oxide, and malondialdehyde (MDA), along with reduced glutathione levels, indicate disruption of redox homeostasis. Similar findings have been reported by Hubel, who emphasized that excessive generation of reactive oxygen species (ROS) due to placental hypoxia–reperfusion injury plays a central role in the pathogenesis of pre-eclampsia [24]. San Juan-Reyes et al. also demonstrated increased lipid peroxidation and altered antioxidant status in pre-eclamptic pregnancies, supporting the oxidative stress hypothesis [34].

In this study, the marked elevation of MDA levels in pre-eclampsia (Table 1 & Graph 1) reflects enhanced lipid peroxidation and oxidative damage to cellular membranes. MDA is a stable end product of polyunsaturated fatty acid oxidation and serves as a reliable indicator of oxidative injury. Comparable increases in MDA levels have been consistently reported in both original studies and meta-analyses, including those by Taravati and Tohidi, who identified MDA as one of the most significantly elevated oxidative stress markers in pre-eclampsia [33]. Afrose et al. further supported the diagnostic relevance of MDA as a biomarker of established pre-eclampsia [35].

Glutathione levels were significantly reduced in pre-eclamptic women in our study (Table 1 & Graph 1), suggesting depletion of a key intracellular antioxidant in response to excessive ROS production. Reduced glutathione plays a crucial role in maintaining cellular redox balance and protecting against oxidative injury. Similar reductions have been reported by Rani et al., who demonstrated decreased placental glutathione levels in pre-eclampsia, indicating impaired antioxidant defense at the maternal–placental interface [36]. Taravati and Tohidi also reported diminished glutathione levels, attributing this finding to sustained oxidative stress and increased antioxidant consumption [33].

Catalase and SOD activities were significantly elevated in pre-eclampsia in our study (Table 1 & Graph 1), suggesting a compensatory upregulation of enzymatic antioxidant defences in response to increased oxidative burden. These enzymes function as first-line antioxidants by detoxifying superoxide radicals and hydrogen peroxide. However, despite this compensatory response, the concurrent elevation of MDA and depletion of glutathione indicate that antioxidant mechanisms are insufficient to

counteract oxidative injury. Similar patterns of elevated antioxidant enzyme activity alongside increased oxidative stress markers have been reported by Onovughakpo-Sakpa et al., highlighting a maladaptive antioxidant response in pre-eclampsia [37].

In this study, nitric oxide levels were significantly increased in women with pre-eclampsia (Table 1 & Graph 1). Although nitric oxide is essential for maintaining vascular tone and uteroplacental perfusion, excessive production under inflammatory and oxidative conditions may result in the formation of peroxynitrite through interaction with superoxide radicals. Peroxynitrite is a potent oxidant capable of inducing lipid peroxidation and endothelial damage, thereby reducing effective nitric oxide bioavailability. Similar mechanisms were described by Guerby et al., who demonstrated oxidative stress–induced endothelial nitric oxide synthase dysfunction in pre-eclampsia [38]. Al-Kuraishy et al. also reported altered nitric oxide metabolism associated with oxidative injury in pre-eclamptic pregnancies [39].

In this study hormonal parameters including estriol, β -human chorionic gonadotropin (β -hCG), and alpha-fetoprotein were significantly elevated in pre-eclamptic women compared to controls (Table 2 & Graph 2), indicating disturbed placental endocrine function. Elevated estriol levels suggest altered placental steroidogenesis, likely secondary to placental hypoxia and oxidative stress. Increased β -hCG levels reflect trophoblastic stress and hypoxic stimulation of placental hormone production, a finding consistent with placental dysfunction in pre-eclampsia. Similar elevations in placental hormones have been associated with hypoxia-induced trophoblast activation and oxidative stress in previous studies [21,40].

The significant rise in alpha-fetoprotein levels in pre-eclampsia in our study (Table 2 & Graph 2) further supports the presence of placental dysfunction and increased placental permeability. Elevated maternal serum alpha-fetoprotein has been linked to placental injury, endothelial dysfunction, and adverse pregnancy outcomes. These hormonal alterations collectively indicate impaired maternal–fetal hormonal regulation and disrupted placental integrity, which contribute to the clinical manifestations of pre-eclampsia.

In our study, general biochemical parameters such as serum ferritin and uric acid were significantly elevated in women with pre-eclampsia (Table 3 & Graph 3). Ferritin, an acute-phase reactant, reflects both iron metabolism and inflammatory activation. The marked elevation of ferritin suggests enhanced inflammatory response and increased oxidative stress, as excess iron can catalyze free radical generation.

Similar findings have been reported in earlier studies, where elevated ferritin levels were associated with disease severity and oxidative stress in pre-eclampsia [28,19].

The serum uric acid levels were significantly higher in our preeclampsia study group pre-eclamptic women (Table 3

& Graph 3), indicating impaired renal function, increased cellular turnover, and heightened oxidative stress. Uric acid is known to accumulate in response to placental ischemia and reduced renal clearance and has been implicated in endothelial dysfunction and inflammation. Elevated uric acid levels have been widely reported as a biochemical hallmark of pre-eclampsia and are associated with disease severity and adverse maternal outcomes [22,28].

In our study, the coexistence of oxidative stress, hormonal disturbances, and biochemical alterations underscores the multifactorial nature of pre-eclampsia. Placental hypoxia and ischemia-reperfusion injury initiate excessive ROS generation, which not only disrupts antioxidant defences but also alters placental hormone synthesis and metabolic regulation. These changes promote endothelial dysfunction, inflammation, and systemic vascular injury, culminating in the clinical syndrome of pre-eclampsia. Similar interactions between oxidative stress, placental dysfunction, and endothelial injury have been emphasized by Hubel and San Juan-Reyes et al. as central mechanisms driving disease progression [24,34].

To conclude in our research work integrated assessment of oxidative stress markers, hormonal parameters, and biochemical indices highlights their collective contribution to the pathophysiology of pre-eclampsia. These findings reinforce the concept that pre-eclampsia is driven by an imbalance between oxidative stress and antioxidant defences, coupled with placental dysfunction and metabolic disturbances, ultimately leading to endothelial injury and adverse pregnancy outcomes.

CONCLUSION

Pre-eclampsia is characterized by significant oxidative stress, hormonal imbalance, and inflammatory-biochemical disturbances. Elevated oxidative stress markers with reduced antioxidant defences indicate impaired redox homeostasis. Increased Alpha fetoprotein, beta-hcg, estriol in preeclampsia reflect placental endocrine dysfunction, while increased ferritin and uric acid signify heightened inflammation and metabolic stress. These abnormalities collectively contribute to endothelial dysfunction and disease progression, highlighting the potential role of integrated biomarker assessment in pre-eclampsia.

CONFLICTS OF INTEREST: None

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