

Endothelin-1 and thyroid hormone dysregulation: potential biomarkers for early detection of pre-eclampsia

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ABSTRACT

Objective: To compare serum thyroid hormones (T3, T4, TSH) and endothelin-1 levels between normotensive and pre-eclamptic pregnant women, and to assess their correlations with systolic blood pressure.

Material and Methods: This comparative cross-sectional study included 140 pregnant women at Liaquat University of Medical and Health Sciences, Jamshoro from November 2021 to April 2022, equally divided into normotensive and pre-eclamptic groups. Baseline demographic and obstetric characteristics were comparable between groups. Serum thyroid hormones and endothelin-1 were analyzed using standard laboratory methods, and data were evaluated with appropriate statistical tests, considering $p \leq 0.05$ as significant.

Results: Pre-eclamptic women exhibited significantly higher blood pressure (SBP 156.43 ± 20.36 mmHg; DBP 103.57 ± 10.05 mmHg, $p = 0.001$). Mean T3 was lower in pre-eclamptic women (1.28 ± 0.4 ng/ml) than controls (2.36 ± 0.3 ng/ml, $p = 0.025$), while T4 remained insignificant ($p > 0.05$). TSH was higher in the pre-eclamptic group (3.76 ± 1.93 IU/ml) compared with normotensive women (2.17 ± 1.81 IU/ml, $p = 0.053$). Endothelin-1 levels were markedly elevated in pre-eclamptic women (53.30 ± 7.78) versus controls (31.89 ± 6.28 , $p = 0.025$). Correlation analysis showed weak **positive associations** of systolic blood pressure with TSH ($r = 0.027$) and endothelin-1 ($r = 0.022$) in pre-eclamptic women, while both markers demonstrated **negative correlations** in normotensive women ($r = 0.016$ and $r = 0.124$, respectively).

Conclusion: Pre-eclampsia is associated with altered thyroid function and significantly increased endothelin-1 levels. These biomarkers show directional correlations with systolic blood pressure and may support early identification of women at risk.

Keywords: Endothelin-1; Pre-Eclampsia; Thyroid Hormones; Pregnancy-Induced Hypertension; Biomarkers

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INTRODUCTION

Pregnancy entails numerous anatomical, physiological and metabolic changes that assure the exchange of proper alliances between the mother and the fetus to promote the growth of the fetus. These changes include hormonal changes, cardiovascular changes, immune modulation and metabolic changes, all of which differ among women depending on genetics, nutrition, socioeconomic status and environment. The maternal system must maintain a finely balanced state in order to provide oxygen, nutrients and hormonal signals to the developing baby. When any of these regulatory mechanisms is disturbed, the risk of obstetric complications is high, of which gestational

hypertensive disorders are a major cause of concern worldwide [1,2].

Pre-eclampsia (PE) is a severe form of gestational hypertension that occurs in about 5-8 per cent of pregnancies worldwide. The incidence among South Asian populations is 0.2 to 9.2 per cent [2,3]. PE is characterized by the development of hypertension after 20 weeks of gestation (systolic >140 mmHg or a diastolic blood pressure >90 mmHg) and proteinuria (urine protein >300 mg/24 h or urine dipstick test $>1+$). Symptoms may include edema, headache and visual disturbances [3]. The condition is associated with systemic endothelial dysfunction, vasoconstriction, oxidative stress and multi-organs involvement, putting both mother and fetus at high risk [4]. Local evidence from a study at LUMHS Hyderabad/Jamshoro gives a prevalence of PE of 10 percent among pregnant women [5].

The pathophysiology of PE starts in the form of abnormal placentation early in pregnancy. The spiral arteries, if not adequately remodeled, result in decreased uteroplacental perfusion, which leads to placental tissues ischaemia and hypoxia [4]. This causes the secretion of anti-angiogenic molecules

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(soluble fms-like tyrosine kinase 1, sFlt-1, and soluble endoglin, sEng) and a decrease in angiogenic molecules (placental growth factor, PlGF, and vascular endothelial growth factor, VEGF), resulting in a severe angiogenic imbalance [6]. The imbalance results in endothelial injury, reduced nitric oxide production and increased vasoconstriction, which are hallmarks of PE.

Thyroid dysfunction is another known factor related to poor obstetric outcomes. Subclinical and overt hypothyroidism occur in approximately 2 to 3 of every 100 pregnant women, and abnormalities in T4 and TSH are common [6-8]. During pregnancy, the physiology of the thyroid changes dynamically because of the increased production of thyroid-binding globulin, elevated requirements for iodine and the suppressive effect of hCG on TSH, especially during the first trimester [9]. Thyroid derangements in hypertensive disorders of pregnancy Studies indicate decreased T3/T4 and increased TSH in women with PE, possibly as the result of impaired placental metabolism or altered maternal-fetal hormone transfer [10,11]. Since thyroid hormones control production of nitric oxide by endothelial cells and vascular smooth muscle tone, hypothyroidism may further promote the vasoconstrictive state of PE [9-11].

A 21 amino acid vasoconstrictor called endothelin -1 (ET -1), which is produced primarily by endothelial cells, has been implicated in the pathogenesis of PE [12]. ET-1 is increased in response to oxidative stress, endothelial damage and placental ischemia; processes that are characteristic of PE. Multiple studies have consistently identified an increase in the circulating concentration of ET-1 is seen in pre-eclamptic women, supporting the role of ET-1 as a mediator of the increased vascular resistance and hypertension [12-14]. ET-1 also interacts with the angiogenic pathways that exacerbate endothelial dysfunction that is central to PE [13]. Matrix metalloproteinases (MMP-1 and MMP-2) metabolize big ET-1 to active ET-1 to enhance PE vasoconstriction.

While international research has been done on thyroid malfunction and ET-1 elevation in PE, there is little local evidence that examines these markers in combination among Pakistani women. Given the high burden of hypertensive disorders in this region, evaluation of these biomarkers is of clinical significance for their early detection and risk stratification. What happens between them may also provide insight into the underlying vascular and endocrine disturbances that contribute to PE.

Therefore, the purpose of this study is to compare serum thyroid hormones (T3, T4, TSH) and endothelin-1 between normotensive and pre-eclamptic pregnant women, as well as their correlation with systolic blood pressure, and thus their potential diagnostic and pathophysiologic relevance in PE.

MATERIAL AND METHODS

This comparative cross-sectional study was carried out in the department of physiology, Liaquat University of Medical and Health Sciences (LUMHS) in collaboration with the department of gynecology and obstetrics and the diagnostic & research laboratory at LUMHS, Hyderabad / Jamshoro. Data collection was carried out during the period of 6 months starting from November 2021 to April 2022 with the approval of synopsis and ethical review committee LUMHS/ERC-143 dated 30th August 2021. A total of 140 pregnant women were enrolled using a non - probability convenience sample. Seventy were preeclamptic women (cases) and seventy were normotensive pregnant women (controls). The sample size was calculated using the RaoSoft calculator, based on an expected local prevalence of 10% in pre-eclampsia, 95% confidence level and 5% margin of error, which resulted into a sample size of minimum 139 and was rounded down to 140 to ensure both groups have the same size [5].

The confidentiality of all participants was preserved throughout the study. The protocol, objectives, possible risks and benefits were explained to the individual participants or their attendants and written informed consent was obtained prior to enrollment.

Participants were women aged between 18-40 years, 20-36 weeks pregnant (confirmed by last menstrual period), including those in their first pregnancy and those with more than 1 pregnancy who attended the Gynecology outpatient department or wards at Liaquat University Hospital, Jamshoro. Women were excluded if they were less than 20 or greater than 36 weeks pregnant, had chronic hypertension, renal disease, thyroid disease and diabetes mellitus, as well as obstetric complications including antepartum haemorrhages and multiple pregnancy and history of thyroid-active medication, corticosteroids, smoking or alcohol use.

A 5 ml venous blood sample was aseptically collected and collected from each participant. Serum was separated and stored under recommended laboratory conditions to analysis. Serum triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) were determined by

electrochemiluminescence immunoassay (ECLIA) using a Cobas e 411 analyser (Roche Diagnostics) with the correction made earlier for an incorrect statement of the methodology used for an immunoassay (ELS) as recommended by reviewers. Endothelin-1 was measured by radioimmunoassay (RIA) after withdrawing serum by column chromatography according to the manufacturer's instructions.

Blood pressure was measured using a calibrated sphygmomanometer. Participants were seated comfortably and rested for at least five minutes before measuring. Pre-eclampsia was diagnosed according to the ACOG diagnosis criteria, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg after 20 weeks of gestation with proteinuria >300 mg/24 h.

Statistical analysis used by the program of the company SPSS version 26.0. Quantitative variables (age, gestational age, BMI, systolic and diastolic blood pressure, T3, T4, TSH, endothelin-1) were expressed as mean plus standard deviation. Categorical variables (parity, group status) were presented as frequencies and as percentages. Normality was tested using the Shapiro-Wilk test. Independent samples t-tests were used to compare group means and chi-square tests were used to compare categorical variables where applicable. Pearson's correlation coefficient (r) was used to test correlations between systolic blood pressure and biochemical parameters. Assumptions of linearity and homoscedasticity were confirmed prior to analysis and statistical significance was determined when p -value was less than 0.05.

RESULTS

A total of 140 pregnant women were enrolled, including 70 (50%) normotensive and 70 (50%) pre-eclamptic participants. The mean age of normotensive women was 28.30 ± 4.96 years, compared with 28.87 ± 4.97 years in the pre-eclamptic group, showing no statistically significant difference ($p = 0.498$). The mean gestational age was 32.01 ± 4.27 weeks in normotensive women and 31.89 ± 4.92 weeks in pre-eclamptic women ($p = 0.799$). Body mass index (BMI) also did not differ significantly between groups, with mean values of

26.49 ± 4.52 kg/m² and 25.94 ± 4.51 kg/m², respectively ($p = 0.724$) (Table-I). Multiparity was observed in 50 (71.4%) normotensive participants and 49 (70%) pre-eclamptic participants. The distribution of parity between the two groups showed no statistically significant difference ($p = 0.154$) (Table-II). Pre-eclamptic women demonstrated markedly elevated blood pressure measurements compared with normotensive women. Mean systolic blood pressure was 117.63 ± 12.25 mmHg in normotensive participants and 156.43 ± 20.36 mmHg in pre-eclamptic participants ($p = 0.001$). Mean diastolic blood pressure was 76.86 ± 8.14 mmHg and 103.57 ± 10.05 mmHg in the respective groups ($p = 0.001$).

These findings show a statistically significant difference consistent with the diagnostic features of pre-eclampsia (Table-III). The mean T3 level was significantly lower in pre-eclamptic women (1.28 ± 0.40 ng/ml) compared with normotensive women (2.36 ± 0.30 ng/ml) ($p = 0.025$). Mean T4 levels did not differ significantly between the two groups ($p > 0.05$). TSH levels were higher in pre-eclamptic women (3.76 ± 0.93 IU/ml) than normotensive women (2.17 ± 1.81 IU/ml); however, this difference did not reach statistical significance ($p = 0.053$) (Table-IV). Endothelin-1 concentrations were significantly elevated in pre-eclamptic women (53.30 ± 7.78) compared with normotensive controls (31.89 ± 6.28), showing a statistically significant difference ($p = 0.025$) (Table-V). In normotensive women, systolic blood pressure showed a very weak negative correlation with TSH ($r = -0.016$), while in pre-eclamptic women, systolic blood pressure had a very weak positive correlation with TSH ($r = 0.027$). The extremely low R-values indicate negligible linear relationships, with no statistical or clinical significance inferred (Figure-I, Figure-III). For endothelin-1, pre-eclamptic women demonstrated a very weak positive correlation with systolic blood pressure ($r = 0.022$), whereas normotensive women exhibited a weak negative correlation ($r = -0.124$). These correlations are minimal in strength and not statistically meaningful (Figure-II, Figure-IV)

Table-I: Demographic data.

Variable	Study groups	Mean	Std. D	p-value
Age (years)	Normotensive	28.30	4.96	0.498
	Pre-eclamptic	28.87	4.97	
Gestational age (weeks)	Normotensive	32.01	3.04	0.799
	Pre-eclamptic	31.89	2.92	
Body mass index (BMI kg/m ²)	Normotensive	26.23	5.02	

Pre-eclamptic	25.94	4.51	0.724
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Table-II: Comparison of parity.

Variable	Study groups		Total	p-value
	Normotensive	Pre-eclamptic		
Parity	MULTI	49	100	0.154
		71.1%	71.4%	
	PRIMI	21	40	
Total		30%	28.57%	
		70	140	
		100.0%	100.0%	

Table-III: Descriptive statistics of blood pressure.

Variable	Study groups	Mean	Std. D	p-value
Blood pressure (systolic) mmHg	Normotensive	122.86	14.797	0.0001
	Pre-eclamptic	156.43	20.362	
Blood pressure (diastolic) mmHg	Normotensive	84.29	7.646	0.0001
	Pre-eclamptic	103.57	10.077	

Table-IV: Descriptive statistics of Thyroid hormone, and Endothelin level.

Thyroid hormone	Study groups	Mean	Std. D	p-value
T3 (ng/ml)	Normotensive	2.36	0.375	0.025
	Pre-eclamptic	1.28	0.470	
T4 (mcg/dl)	Normotensive	11.51	2.076	0.623
	Pre-eclamptic	10.33	2.248	
TSH (IU/ml)	Normotensive	2.17	1.819	0.0538
	Pre-eclamptic	3.76	0.934	

Table-V: Descriptive statistics of endothelin level

Variable	Study groups	Mean	Std. D	p-value
Endothelin level	Normotensive	31.89	6.288	0.025
	Pre-eclamptic	53.30	7.784	

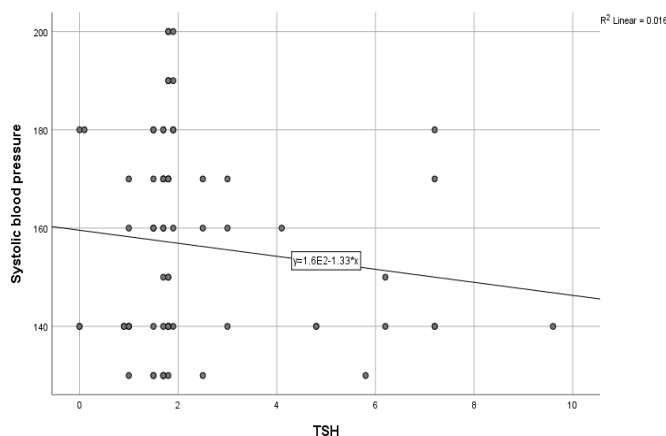
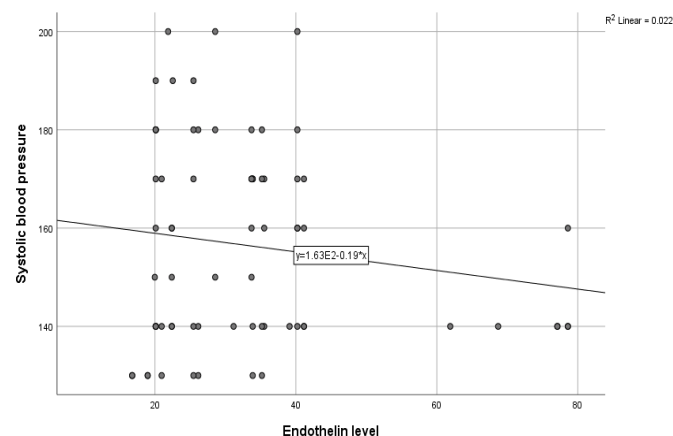
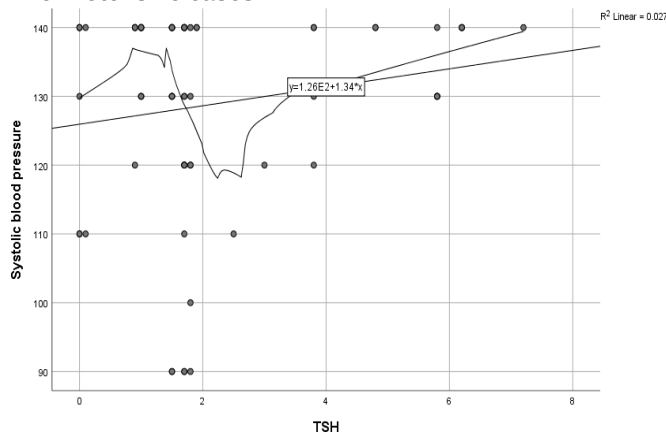
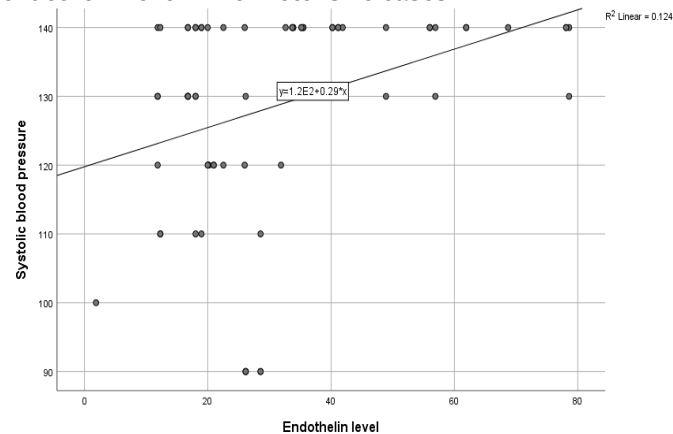
**Figure-I: Correlation of systolic blood pressure with TSH in normotensive cases.****Figure-II: Correlation of systolic blood pressure with endothelin level in normotensive cases.**

Figure-III: Correlation of systolic blood pressure with TSH in pre-eclamptic cases.**DISCUSSION**

Pre-eclampsia is a multiorgan disease characterised by endothelial dysfunction, vasoconstriction, and disturbances of biochemical homeostasis, and demonstrates pathophysiologic features observed in prior studies [15,16]. In this sample, women with pre-eclampsia had significantly lower T3 and significantly higher endothelin 1 levels than normotensive pregnant women; T4 and TSH levels were not significantly different. Blood pressure was also higher in pre-eclamptic participants but correlations between systolic blood pressure and these biochemical markers were weak and were not statistically meaningful. Together, these findings highlight the interplay between the hormonal and vascular disruptions in pre-eclampsia.

Lower T3 levels in pre-eclamptic women are consistent with findings from previous studies reporting on a "low T3 syndrome" or non-thyroidal illness pattern of illness in hypertensive disorders of pregnancy [17-19]. This may be related to the impaired conversion of T4 to T3 in the peripheral system as a result of impaired activity of the placental type-II deiodinase, changes in maternal metabolism, and increased oxidative stress⁽²⁰⁾. Although TSH was higher, the difference was not statistically significant ($p = 0.053$), indicating that the changes are due to stress in the metabolism and blood vessels and not actual hypothyroidism. Similar mild elevations in TSH with normal T4 have been noted from Pakistan and India as well, consistent with a hypothesis of compensated or secondary thyroid changes [21,22]. Endothelin1 concentrations were significantly elevated in pre-eclamptic women highlighting its established role in endothelial injury and severe vasoconstriction [28, 24]. Placental ischemia, oxidative stress and anti-angiogenic imbalance are responsible for ET-1 production, making it an important mediator of vascular dysfunction in pre-eclampsia [25]. Upregulation of matrix metalloproteinases (MMP-1 and MMP-2) increases conversion of big ET-1 to active ET-1, which increases vasoconstrictive responses [27, 28]. International and regional studies are also reporting high ET-1 levels among pre-eclamptic women, strengthening the case for this marker as a biomarker of endothelial dysfunction [28,30]. The significantly higher concentrations of ET-1 in our population further supports the use of ET-1 as an early marker for the identification of women at risk of developing pre-eclampsia.

Figure-IV: Correlation of systolic blood pressure with endothelin level in pre-eclamptic cases.

Unlike some international studies that found moderate correlations between ET-1 and blood pressure, our study showed negligible associations, with R-values close to zero ($r = 0.027$ in pre-eclamptic women and $r = -0.124$ in normotensive women). These weak correlations suggest that the multifactorial regulation of blood pressure in pregnancy cannot be explained by any single biomarker that involves the endocrine, renal, autonomic, and vascular pathways [31,32]. Sample size limitations, physiologic variability among pregnant women, and single time point sampling are likely to have contributed to weak correlation patterns.

Our results agree with previous studies in Pakistan, India, Bangladesh, and Middle East, which also found decreased T3 and increased endothelin-1 in pre-eclamptic women, however, the extent of disruption varies from one population to the other [21, 22, 28]. Variability may be due to differences in genetics, iodine intake, nutritional status, socioeconomic factors and laboratory methods [33]. Gestational age at sampling and severity of the disease at presentation are also likely causes of heterogeneity between studies worldwide.

The major strength of the study was simultaneous measurement of thyroid hormones and endothelin-1 by validated biochemical assays (ECLIA and RIA) in well matched groups of pregnant women. Matching for maternal age, gestational age, and BMI controlled for demographic confounding to increase internal validity.

LIMITATIONS

The cross-sectional design has a limitation when it comes to making causal inferences. Although the sample size detected group differences it may have been underpowered for subtle correlations. The single-centered setting limits the generalizability. Variability in the concentration of endothelin-1, caused by circadian rhythm, stress or handling, was uncontrolled. Future multicenter, longitudinal studies are necessary to confirm the validity of these findings and assess the predictive utility.

CLINICAL IMPLICATIONS

Despite limitations, the results indicate that endothelin-1 is a promising early biomarker for identifying women at risk for pre-eclampsia, particularly in resource-limited settings where maternal morbidity is high. Mild thyroid hormone

changes may give supportive insight in metabolic adaptation under vascular stress. Incorporating these biochemical markers in antenatal risk assessment frameworks could lead to better detection and individual monitoring of high-risk pregnancies in earlier stages.

CONCLUSION

While endothelin-1 levels were elevated in pre-eclamptic women, the observed correlations with systolic blood pressure were weak, indicating limited linear association. Therefore, endothelin-1 may be better interpreted as a marker of endothelial activation rather than a direct indicator of blood pressure magnitude.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Declared none

AUTHORS CONTRIBUTION

Moomal Tagar: Substantial contributions to study design, acquisition of data, manuscript drafting, reviewing it critical for important intellectual content, final approval, accountable for all aspects of publication.

Salma Farrukh: Substantial contributions to study design, acquisition of data, Data curation, statistical analysis, supervision, final approval, accountable for all aspects of publication

Sarwat Batool: Manuscript drafting, final approval, accountable for all aspects of publication.

Shahzad Tariq: Critical review, final approval, accountable for all aspects of publication.

Rabia Bughio: Revisions, final approval, accountable for all aspects of publication.

Rizwan Talpur: Statistical analysis, final approval, accountable for all aspects of publication.

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