Association Between Thyroid Dysfunction and Pre-Eclampsia with Severe Features

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Abstract

Background: The physiological changes in the thyroid gland during pregnancy are well understood but only a few reports provide information about thyroid function in complicated pregnancies, like preeclampsia with severe features, especially from Bangladesh. Hence this study was done to establish an association between thyroid dysfunction with preeclampsia with severe features in our population.

Materials and methods: In this case-control study, 50 preeclamptic women with severe features (Case) and 50 normotensive pregnant women (Control) were selected from the Obstetrics & Gynecology Department of Chittagong Medical College Hospital. Thyroid profile (Free triiodothyronine [FT3], Free thyroxine [FT4] and Thyroid Stimulating Hormone [TSH]) was measured by the Chemiluminescent Immunoassay (CLIA) technique.

Results: The mean serum TSH level in cases was increased significantly than in the control (3.69±1.32 mIU/L versus 2.42±0.96mIU/L,p<0.001). Serum T3 (2.51±0.26 Pg/ml versus 2.70±0.43pg/ml, p=0.006) and T4 levels (1.0±0.28 ng/dl versus 1.12±0.23ng/dl,p=0.024) were decreased significantly in preeclamptic women when compared to controls. Thirty-eight per centof the preeclamptic women had TSH titers>4mIU/ml as compared to 8% in the controls (p<0.001). The odd ratio corresponding to TSH titers> 4mIU/ml in preeclamptic women with severe features was 3.44 (95%, CI=1.38-8.53).

Conclusions: These results indicate that thyroid function is altered in preeclampsia with severe features and pregnancy with hypothyroidism are more susceptible to develop Pre-eclampsiawith severe features .

Key words: Free thyroxine; Free triiodothyronine; Pre-eclampsia; Thyroid-stimulating hormone.

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Introduction

Thyroid diseases including hypothyroidism, hyperthyroidism and Subclinical Hypothyroidism (SCH) with various etiologies are some of the most common diseases experienced by reproductive-aged women. During pregnancy, hypothyroidism including Overt Hypothyroidism (OH) and SCH are the most frequent thyroid dysfunctions being present in approximately 0.4% (OH) to 3% (SCH) of pregnant women but it is believed that they are more common than generally acknowledged.[1-3] The range of prevalence of undiagnosed SCH during pregnancy has been estimated to be even higher from 3% up to 15% with the difference being attributable to the various diagnostic criteria.[4] Preeclampsia (PA) is a possible pregnancy-related complication in women with hypothyroidism.[2-5] In its most severe cases, preeclampsia may cause serious organ damage and fetal growth restriction leading to preterm birth and increased risk of neonatal morbidity and mortality. This disease encompasses 2% to 8% of pregnancy-related complications, greater than 50,000 maternal deaths and over 500,000 fetal deaths worldwide.[6] Severe and early-onset preeclampsia, as well as thyroid dysfunction, are associated with a higher risk of preterm birth and low neonatal birth weight.[7] Globally the incidence of preeclampsia is approximately 5-15% of pregnancies, although the risk is assumed to be higher in developing countries.[8] Despite advances in reducing child and infant mortality, preeclampsia and eclampsia-related mortality constitute a significant concern in Bangladesh. Each year in Bangladesh, 5,000 and 6,000 women die during pregnancy or childbirth, and up to 24 per cent of those deaths

are from eclampsia.[9] A recent study reported that 44% of the 3rd trimester pregnant women who visited a Maternity Clinic in Dhaka city suffered from PE.[10] Preeclampsia is a serious pregnancy complication with unknown aetiology that may occur at any stage of the second or third trimester. Although it is defined in terms of hypertension and proteinuria, it can affect other maternal systems, so the presentation and progression of this disease are variable. Furthermore, the treatment of this disorder has not significantly changed from 50 years ago. The cause of preeclampsia has remained unknown but the condition has been reported to be correlated with some factors. Thyroid dysfunction is one of those factors which were found to be related to preeclampsia. However, controversy prevails to date regarding this association. Though there is no consensus guideline regarding assessing thyroid function in pre-eclampsia with severe features. If thyroid dysfunction is associated with pre-eclampsia with severe features, early treatment of thyroid dysfunction will help to prevent pre-eclampsia-related morbidity and mortality. There was a scarcity of studies assessing the association between thyroid dysfunction and pre-eclampsia with severe features, especially in the late third trimester of pregnancy. The aetiology of pre-eclampsia is heterogeneous.[11] In some previous studies, women with thyroid diseases (Mostly hypothyroidism) have had a higher risk of developing pre-eclampsia during an ongoing pregnancy.[12,13] The association between hypothyroidism and increased prevalence of pre-eclampsia existed even after propensity score matching for other common risk factors for pre-eclampsia.[12] Normal pregnancy is associated with important and complex changes in maternal thyroid physiology and hormone production and maternal and fetal thyroid hormone profiles change as gestation progresses. During the first trimester, normal thyroid function increases Thyroxine (T4) and Triiodothyronine (T3) production and subsequent inhibition of Thyroid-Stimulating Hormone (TSH) in part due to the production of high concentrations of human chorionic gonadotrophin, which stimulates the TSH receptor.[14] Previous studies have tested the association between thyroid hormone status and pre-eclampsia, but the results have been controversial. Some of study have even reported negative results.[15-18] Hence, the present study aimed to test the thyroid profile in pre-eclampsia with severe feature patients and normal pregnant ladies to determine the association in between the thyroid dysfunction in pregnancy. There is no such study done in Chattogram, Bangladesh. The aim of the study was to compare the thyroid status between patients with pre-eclampsia with severe features and normotensive pregnant women.

Materials and methods

This is a case-control study, 100 patients were enrolled and analyzed in this study. The study was conducted at the Department of Obstetrics & Gynecology, Chittagong Medical College Hospital (CMCH) Chattogram, Bangladesh. The study duration was one year from July 2021 to June 2022.The ethical approval was taken from the Ethical Review Committee of Chittagong Medical College. Admitted normotensive and preeclampsia with severe featurepregnant women>28 weeks at the Obstetrics & Gynecology Department of CMCH during the study period. Patients were randomly selected into two groups; Group A and Group B, each group have 50 patients.

Group A (Case): Pregnant women with preeclampsia with severe features.

Group B (Control): Normotensive pregnant women.

Inclusion criteria

- Preeclamptic woman having severe features of pre-eclampsia with thyroid dysfunction (Case group)
- Pregnancy with hypothyroidism
- Normotensive pregnant woman (Control group)
- Age between 16-45 years
- Gestational age more than 28 weeks of pregnancy.

Exclusion criteria

- History of multiple pregnancies, chronic hypertension, other cardiovascular disorder, diabetes mellitus, renal disease, autoimmune disease
- Patients who did not give consent for the study.

An equal number of age and gestation-matched healthy normotensive pregnant women in the third trimester admitted at the Obstetrics & Gynaecology Department of CMCH during the study period constituted the comparison group.

Preeclamptic women with severe features and normotensive pregnant women were selected as per the mentioned inclusion and exclusion criteria. After obtaining written informed consent, necessary clinical data were collected as per the case record form. Detailed socio-demographic data, obstetric history, gestational age, family history and medical history were recorded in a predesigned data sheet. The physical examination was performed and recorded. After 10 minutes of rest, blood pressure was measured following standard procedure. Korotkoff phase 1 (First beat heard) and phase V (Disappearance of sound) was used to determine systolic and diastolic blood pressure. When blood pressure was found elevated on the initial assessment, the measurement was repeated at least 4 to 6 hours apart to confirm hypertension. Proteinuria was measured by the dipstick method. After taking aseptic precaution, five millilitres of venous blood sample was taken from the median cubital vein. The thyroid profile was measured using Chemiluminescent Immunoassay (CLIA). After collection, data were entered into a Microsoft Excel datasheet to generate a master sheet. Then the data were fed into SPSS version-23 for processing and analysis. According to their distribution, continuous data were expressed as either mean (±Standard deviation). Differences in mean values between the pre-eclampsia with severe features and normotensive pregnancy groups were tested using the independent sample t-test. Categorical data were expressed as frequency (Percentages) and compared between two groups either by Chi-square test or Fisher's exact test as appropriate. The strength of the association between abnormal thyroid hormone status and preeclampsia was expressed by Odds Ratio (OR) with a 95% Confidence Interval (CI) for OR. p <0.05 was considered as statistical significance.

Results

In the present study, one hundred pregnant women were included (50 with preeclamptic women with severe features and 50 with normotensive pregnancy). FT3, FT4, and TSH levels were compared between these two groups.

Table I Sociodemographic characteristics of study subjects stratified by study groups

Variables	Group A		Group B		p value
	n	%	n	%	
Age groups (Years)					
<20	8	16.00	4	8.00	0.368
20-29	32	64.00	32	64.00	
30-39	10	20.00	14	28.00	
Socio-economic class					
Lower	37	74.00	36	72.00	0.822
Lower middle	13	26.00	14	28.00	
Residence					
Rural	43	86.00	39	78.00	0.298
Urban	7	14.00	11	22.00	

In the present study, one hundred pregnant women were included (50 with preeclamptic women with severe features and 50 with normotensive pregnancy). FT3, FT4, and TSH levels were compared between these two groups.

Table II Distribution of obstetric characteristics between groups

Variables	Group A		Group B		p value
	n	%	n	%	
Gravida					
Primi	28	56.00	16	32.00	0.016
Multi	22	44.00	34	68.00	
Gestational age (weeks)					
28-32	7	14.00	0	0.00	<0.001
33-36	21	42.00	8	16.00	
>37	22	44.00	42	84.00	

Data were expressed as frequency (%);*p values were obtained from the Chi-square test.

The majority of the women withPre-eclampsia with severe features were primigravid (56.0%). Most of the women in both groups had gestational age 37 weeks and more. However, significantly higher proportion of the preeclamptic women with severe featurewere in 28-32 weeks, and 33-36 weeks of gestation than the normotensive group (p<0.001).

Table III Physical examination findings between groups

Parameters	Group A	Group B	p value
Height (cm)	150.4±2.	151.3±3.7	0.119
Weight (kg)	82.7±5.3	79.±3.8	0.007
BMI (kg/m2)	28.9±2.2	28.1±1.8	0.013
SBP (mm Hg)	164.2±22.9	115.1±9.9	<0.001
DBP (mm Hg)	107.3±16.3	74.9±8.4	<0.001

The mean weight, BMI, systolic and diastolic blood pressure were significantly higher in preeclamptic women with severe features compared to normotensive women (Table III).

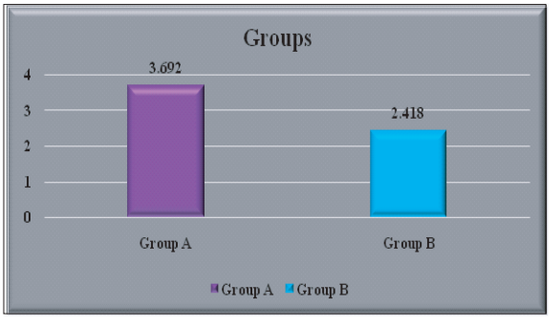

Figure 1 Bar diagram comparing mean serum TSH levels between preeclamptic women with severe features and normotensive pregnant women

The mean (±SD) TSH level was found to be significantly higher in the preeclamptic women with severe feature than the normotensive pregnant women (3.69±1.32 mIU/L versus 2.42±0.96mIU/L, p<0.001) (Figure 1).

Table IV Abnormal thyroid hormone status between preeclamptic pregnancy with severe feature and normotensive pregnancy group.

Variables	Group A		Group B		Odds ratio (95% CI for OR)	p value
	n	%	n	%		
				TSH		
0.4-4.0 mIU/L	31	62.00	46	92.00	3.44 (1.38-8.53)	<0.001*
>4.0 mIU/L	19	38.00	4	8.00		
				FT3		
2.16-3.63 pg/ml	47	94.00	50	100.00	3.19(0.32-31.77)	0.242†
<2.16 pg/ml	3	6.00	0	0.00		
				FT4		
0.8-1.8 ng/dl	45	90.00	49	98.00	3.13(0.52-18.92)	0.204†
<0.8 ng/dl	5	10.00	1	2.00		

Out of 50 preeclamptic patients with severe feature, 19 (38%) have subclinical hypothyroidism compared to 4 (8.0%) out of 50 normotensive pregnant women and the difference was highly significant statistically. The OR for SCH among preeclampsia with severe feature was 3.44 (95% CI = 1.38-8.53), when compared to normal pregnant women (Table IV). Proportion of the participants with low FT3 and low FT4 levels were higher in pre-eclampsiawith severe features group than the normotensive pregnancy group, but the differences failed to reach statistical significance (p>0.05).

Discussion

The present study findings were discussed and compared with previously published relevant studies.The age range of the preeclamptic women was divided into three categories 16% of respondents were below 20 years, 64% were 20 to 29 years and about 20% were in the 30 years and above age group. This age distribution of the preeclamptic women agreed with a recent study from Bangladesh where the majority of the patients (75%) were in the 20 to 29 years age group.[10] The age distribution of the preeclamptic patients of the present study was also comparable to the other studies conducted in our neighbouring countries.[19-20] As generally in public hospitals people from low to lower middle socioeconomicstrata take their services, it can be assumed that the majority are from poorer sections of society. In the current study, 74% of the cases belong to the low socio-economic class. Similarly, 86% of the patients came from rural areas. These socio-demographic characteristics of the preeclamptic patients were similar to other studies conducted in public hospitalsin Bangladesh.[10] In the present study, the mean (±SD) serum TSH level was 3.69±1.32mIU/L for the patients with preeclampsia with severe features and 2.42±0.96 mIU/L for those with normotensive pregnancy. The mean difference was found to be highly significant statistically (p<0.001). Muraleedharan et al. reported that TSH was significantly higher in severe cases when compared to mild cases as well as normal pregnancies.[21] TSH was significantly higher even in mild cases when compared to normal pregnancy. Lao et al. did not find a significant reduction in preeclamptics, but severe preeclamptics had significantly reduced TSH than mild preeclamptics.[22] Some study also found that TSH increased significantly in severe compared to mild PE.[19,21,23,24] Contrary to these findings and the findings of the present study, the study of Khadem et al. suggests that the TSH level was not significantly different between preeclampsia and normal pregnancy.[16] A study from Qublan et al. performed on 27 severe preeclampsia cases reported that no significant difference was observed in TSH level between preeclamptic cases and normal pregnant groups with various gestational age subgroups.[15] Other than the small sample size, this difference in the results may be because the time of blood sample was different in the studies; a high level of TSH would be observed at a later stage of preeclampsia. In the

present study, it was found that preeclamptic cases with severe features had significantly lower FT3 and FT4 than normal pregnant ladies. Muraleedharan et al. found that severe cases of PE had significantly lower T3, T4, FT3, and FT4 than normal pregnant ladies, but not when compared to mild cases.[21] Sardana et al. also did not find a significant reduction in T3 and T4 between severe and mild cases.[24] Ashok et al. tested FT3 and FT4 only, but they were within the expected range both in preeclamptic women and normotensive pregnant women.[25] Qublan et al. and Khadem et al. did not get a significant decrease.[15,16] The findings of a significant decrease in FT3 and FT4 levels and an increase in TSH levels in preeclampsia with severe features as compared to normotensive controls indicatehypo-functioning of the thyroid gland. For the prevention of preeclampsia, it becomes necessary to know the pathogenesis and factors that modify the course of the disease and its complications. Identification of thyroid abnormalities and appropriate measures might affect the occurrence and severity of morbidity and mortality associated with severe preeclampsia. Present findings suggest that primary hypo-functioning of the thyroid can accompany pre-eclampsia with severe features and possibly contribute to the pathogenesis.

Limitation

Every hospital-based study has some limitations and the present study undertaken is no exception to this fact. The limitations of the present study are mentioned. Samples were selected conveniently from a single tertiary care hospital located in the southeastern part of Bangladesh. Another limitation was the late gestational age at sampling across the two groups in the majority of the cases. The thyroid profile of the participants was measured at the same time as the PE status. So, the temporal association between these two variables was not explainable by this study design. Absence of a group of pre-eclampsia without severe features.

Conclusion

The present study indicates that TSH level is increased in preeclamptic patients with severe features than in normotensive pregnant women. Subclinical hypothyroidism is associated with pre-eclampsia with severe features. In a word, patients with thyroid dysfunction are more susceptible to developpre-eclampsia.

Recommendation

It emphasizes the monitoring of thyroid hormone levels during the antenatal period. Thyroid profiles could be checked in the second and third trimesters in preeclamptic patients having severe features. However, to suggest the measurement of serum levels of FT3, FT4 and TSH as a tool for the prediction of preeclampsia with severe features and to establish thyroid hypofunction as a possible aetiology for preeclampsia with severe features further large-scale prospective studies are needed.

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Contribution of authors

LD-Conception, acquisition of data, data analysis, manuscript writing & final approval.
MZ-Acquisition of data,manuscript writing & final approval.
SS-Data analysis, interpretation of data & final approval.
MB- Acquisition of data, manuscript writing & final approval.
TT-Acquisition of data, data analysis, critical revision of version & final approval.
FA-Acquisition of data,data analysis,critical revision of version & final approval.
KS-Data analysis, critical revision of version & final approval.
FIC-Interpretation of data, critical revision of version & final approval.
FR-Design, data analysis, manuscript writing & final approval.
SA-Conception, design, critical revision of version & final approval.

Disclosure

All the authors declared no conflict of interest.

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