An Evaluation of Thyroid Function in Preeclampsia

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Abstract

Background: Pregnancy is associated with reversible physiological changes in thyroid function which is well documented. These changes in thyroid function have been considered as one of the pathophysiological causes of preeclampsia. Pre-eclampsia is an elusive condition to diagnose and a complex disease to manage. The aim of the study is to determine the association of reduced thyroid function with preeclampsia.

Materials and methods: This cross sectional study was carried out in the Department of Obstetrics & Gynecology. Bangabandhu Sheikh Mujib Medical University, Dhaka between October 2015 and August 2016. A total of 70 pregnant women between 18 and 35 years of age attending outdoor antenatal clinic were enrolled in this study. Among them 35 pregnant women with clinical diagnosis of preeclampsia were considered as case and group I, and rest 35 apparently healthy normotensive pregnant women were considered as control and group II. Blood samples were collected and estimated for TSH and FT_4. Statistical analysis of the results was obtained by using Windows based computer software devised with Statistical Packages for Social Sciences (SPSS-22).

Results: The mean TSH levels were significantly higher ($p<0.05$) in preeclampsia (4.8±3.1 μIU/ml) group as compared to control (2.2±1.1 μIU/ml) group but no significant difference was found in mean FT_4 levels between the groups. The odds ratio corresponding to TSH level >3.5 μIU/ml in preeclamptic women was 3.8 (95% CI 1.2 to 11.6%). Significant positive correlations were found between TSH levels with systolic blood pressure, diastolic blood pressure and proteinuria in preeclampsia group ($r=0.550$, $p=0.001$, $r=0.644$, ($p=0.001$) and $r=0.618$, $p=0.001$ respectively).

Conclusion: Abnormal TSH titer is associated with the risk of occurrence of preeclampsia and its severity.

Key words: Free Thyroxine (FT_4); Preeclampsia; Thyroid Stimulating Hormone (TSH).

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Introduction

Hypertensive disorders of pregnancy complicate 10% of all pregnancies and are estimated to cause 40,000 maternal deaths worldwide each year.[1,2] Preeclampsia is a pregnancy specific hypertensive disease with multisystem involvement. It is still a major obstetric problem in medical practice which affects maternal health and puts fetal development atrisk.Preeclampsia has been estimated at 10% of the pregnant population.[3] The most devastating complication in pre-eclampsia is maternal death.[4] Overall, 10% to 15% of direct maternal deaths are associated with preeclampsia and eclampsia both in developed and developing countries. The International Society for the Study of Hypertension in Pregnancy published updated guidance on the diagnosis and management of hypertensive disorders of pregnancy in 2018. The revised definition of pre-eclampsia is de novo hypertension after 20 weeks gestation with one or more of proteinuria, maternal organ dysfunction (Including renal, hepatic, hematological or neurological features) or fetal growth restriction.[5] The disease may be mild or may cause serious maternal morbidity and mortality such as cerebrovascular accidents, seizure, cerebral edema, pulmonary edema, hepatic failure, renal failure, disseminated intravascular coagulation or placental abruption.[6] Pre-eclampsia has long-term health implications for women and increases lifetime risk of cardiovascular disease.[7] Furthermore, preeclampsia and its outcome have a higher risk of chronic noncommunicable diseases

(NCDs) in later life such as hypertensive disorder, renal disease and thus causes double burden to the health sector and limited resources in the developing countries.[8] Fetal and neonatal consequences include intrauterine growth restriction, stillbirth, severe iatrogenic prematurity due to delivery for maternal indication as the only known treatment of preeclampsia is delivery, after which symptoms usually resolve.

Preeclampsia is a disease of unknown etiology which makes its prevention and management an ongoing challenge worldwide.[9] Several theories, including inadequate placental implantation, immune response and angiotensin II sensitivity, have been proposed.[6] Placental hypoxia, ischemia, excessive oxidative stress, and endothelial cell dysfunction characterize the disease. Release of soluble factors from the ischemic placenta into maternal plasma plays a central role in the ensuing endothelial dysfunction that is the most prominent feature of this disease.[10]

Although the exact mechanisms, which lead to preeclampsia are not clear, several factors are known to play a part in determining pregnant women who are at risk of the disease. These are primiparity, previous preeclamptic pregnancy, chronic hypertension or chronic renal disease, history of thrombophilia, multiple gestation, in vitro fertilization, family history of preeclampsia, diabetes mellitus, obesity, systemic lupus erythematosus, advanced maternal age.[11]

Despite the modern advancement in the medical technology, there is no well-established measure for prevention of preeclampsia in the general population and treatment is largely symptomatic.[12] The curative treatment is being delivery, management needs continuous balancing between risk of prematurity of fetus with the risk of maternal morbidity and mortality.[13] Preeclampsia that might lead to a future treatment other than delivery, allow definitive diagnosis, open avenues for consistent research, enable the monitoring of effective treatments.[6]

Pregnancy is a physiological process, maternal physiological adjustments of different organ system occur in pregnancy. Pregnancy has a profound and reversible effect on the thyroid gland. During pregnancy there is an increased thyroid demand, iodine uptake and synthesis of thyroid hormones. There is two to three-fold increase in production of TBG and a 30-40% increase in total triiodothyronine and thyroxine concentration, increase in thyroglobulin and increase iodide clearance. The placenta also releases several thyroid stimulatory factors e.g. HCG. Alpha sub unit of HCG is identical to that of TSH and has a mild thyroid stimulating activity. In preeclampsia there is failure of estrogen production due to placental dysfunction, resulting in lowering in TBG, TT_3 and TT_4. In the circulation whole T_4 originates from thyroid secretion but most T_3 (80%) is produced extrathyroidally from deiodination of T_4.[14] Liver, kidney and brain are affected due to autointoxication in preeclampsia and functional disorders in these organs are evident as well. As liver, kidney and muscles are the main organs of deiodination of T_4 to T_3 the serum concentration of T_4 and T_3 may be different in preeclampsia than in normal pregnancy.[15] Moderate decrease in thyroid hormones with concomitant increase TSH levels in maternal serum correlated with severity of preeclampsia or eclampsia. These changes in thyroid function might be consequences of the dysfunction in the hypothalamic-pituitary-thyroid axis, secondary to disease itself .

Studies regarding thyroid function test in preeclampsia are scanty and controversial. Serum thyroid function test is simple, reliable, economic and sensitive.This can now be considered as an adjunct for early diagnosis and treatment of preeclampsia to prevent further complications.[16]

The present study was designed to clarify the status of thyroid profile in preeclampsia and aimed to find out its association with the occurrence and severity of preeclampsia. Detection of relation between altered thyroid function and preeclampsia will help us to predict such a serious condition early, many preventive measures can be taken to reduce both maternal and fetal morbidity and mortality.

Materials and methods

This cross sectional study was carried out in the Department of Obstetrics & Gynecology, Bangabandhu Sheikh Mujib Medical University, Dhaka between October 2015 and August 2016. Ethical clearance for the study was taken from the institutional review board, BSMMU. A total of 70 pregnant women between 18-35 years of age attending outdoor antenatal clinic were enrolled in

this study. Among them 35 pregnant women with clinical diagnosis of preeclampsia were considered as case and group I, rest 35 apparently healthy normotensive pregnant women were considered as control and group II. Pregnancy with chronic hypertension, Pregnancy Induced Hypertension (PIH) without proteinuria, DM, GDM, Multiple pregnancy, maternal history of taking antithyroid drug, previous history of any thyroid disorder, thyroid surgery, chronic renal disease, chronic liver disease were excluded from this study. Purposive sampling was done according to the availability of the participants who had voluntarily joined this study. The purpose and procedure of study was discussed with the participants and informed written consent was taken. An interviewer administered questionnaire was used for data collection. Detailed socio-demographic data, obstetric history, menstrual history (LMP) to calculate gestational age, family history and medical history were recorded in a predesigned data sheet. Then physical examination, anthropometric measurements (Height, weight) were taken and obstetric examination were performed and recorded. After 10 minutes of rest, BP was measured following standard procedure for systolic (SBP) and diastolic (DBP). The BP was measured on right arm, with the patient sitting comfortably, legs uncrossed and back and arm supported or lying on her back 45 to the horizontal. In both the cases the occluded brachial artery was kept at the level of the heart. When blood pressure was found elevated on initial assessment, the measurement was repeated at least 4 to 6 hours apart to confirm hypertension. The subjects with blood pressure ≥ 140/90 mm of Hg on two occasions were evaluated for 24-hours urinary total protein to establish the diagnosis of preeclampsia. When proteinuria found 300mg or more in a 24 hours' urine collection then the diagnosis of preeclampsia was established and they were selected as cases. The subjects who were found normotensive were selected as control. Cases and controls were matched for age, parity and gestational age. After selecting cases and controls 5ml of ante-cubital fasting venous blood sample was collected from each subjects with all aseptic precaution for measurement of TSH and FT_4. Serum TSH and FT_4 levels were measured with Siemens ADVIA Centaur XP Immunoassay system by Chemiluminescent Immunoassay (CLIA) technology in the Immunology and Microbiology laboratory of BSMMU. According to American Thyroid Association and American Association of Clinical Endocrinologist guidelines (2012) normal range of TSH value in third trimester of pregnancy is 0.3-3.5 μIU/ml. So in this study TSH value >3.5 μIU/ ml was considered abnormal.[17] Statistical analysis of the results was obtained by using Windows based computer software devised with Statistical Packages for Social Sciences (SPSS-22).

Results

35 pregnant women with the diagnosis preeclampsia attending the antenatal clinic of the department and fulfilling the inclusion and exclusion criteria were evaluated for serum TSH and FT_4 concentration and the findings were compared with equal no of age, parity and gestational age matched normotensive pregnant controls who fulfilled the inclusion and exclusion criteria. The observations and results of the study are presented below:

Table I Distribution of the study subjects according to parity (n=70)

Para	Case (PE) Group (n=35)		Control Group (n=35)		χ^2value	p value
	n	%	n	%		
Nulliparous	23	65.7	22	62.9	0.06	0.803^{ns}
Multipara	12	34.3	13	37.1		

Table I shows that almost two third patients were nulliparous in both PE (65.7%) and in normal pregnant (62.9%) groups. The difference was not statistically significant (p>0.05) between two groups.

Table II Distribution mean TSH & FT_4 levels among the study groups (n=70)

Thyroid function test	Case (PE) Group (n=35) Mean ±SD	Control Group (n=35) Mean ±SD	t value	p value
TSH (μIU/ml)	4.8±3.1	2.2±1.1	4.676	0.001^{s}
Range (Min-max)	0.59-12.7	0.70-6.6		
FT_4 (ng/dl)	1.15±0.14	1.23±0.21	1.875	0.065^{ns}
Range (Min-max)	0.8 -1.40	0.81 -1.67		

Table II shows that mean TSH was found 4.8±3.1 μIU/ml in preeclampsia group and 2.2±1.1 μIU/ml in control group. The mean FT_4 was found 1.15±0.14 ng/dl in preeclampsia group and 1.23±0.21 ng/dl in control group. The mean TSH

was significantly higher (p<0.001) as compared to control group. In both the group all FT_4 values were found within normal range (0.81.8 ng/dl) but

Table III Distribution of normal and abnormal TSH levels among the study Groups (n=70)

TSH (μIU/ml)	Case Group (n=35)		Control Group (n=35)		OR (95% CI)	χ^2 value	p value
	n	%	n	%			
>3.5 μIU/ml	21	60.0	10	28.6	3.8 (1.2-11.6)	7.01	0.008^s
≤3.5 μIU/ml (Normal)	14	40.0	25	71.4			

OR= Odds Ratio.

Table III shows that 21(60.0%) patients were found to have TSH level >3.5 μIU/ml in the preeclampsia case group and10 (28.6%) in the control group. So, 21(67.74%) women out of total 31 pregnant women with abnormal TSH titers, had the diagnosis of preeclampsia, whereas only 14 (28.57%) of the 49 pregnant women with normal TSH titers had preeclampsia in third trimester. The difference between the two groups was found statistically significant (p<0.05). The odds ratio was 3.8 which indicate if the TSH titer >3.5 then the risk of developing preeclampsia is 3.8 times higher (95% CI 1.2 to11.6).

Table IV Distribution of TSH and FT_4 in mild and severe PE cases (n=35)

Thyroid function test	Preeclampsia		t value	p value
	Mild preeclampsia (n=13) Mean±SD	Severe preeclampsia (n=22) Mean±SD		
TSH (IU/ml)	2.95±1.2	5.82±3.43	2.90	0.006^s
Range (Min-max)	0.59-4.69	1.65-12.7		
FT_4 (ng/dl)	1.16±0.12	1.14±0.16	0.39	0.699^{ns}
Range (Min-max)	0.91-1.3	0.8 -1.4		

Table IV shows mean TSH was 2.95±1.2 μIU/ml in mild preeclampsia and 5.82±3.43 μIU/ml in severe preeclampsia. The mean FT_4 was 1.16±0.12 ng/dl in mild preeclampsia and 1.14±0.16ng/dl in severe preeclampsia. The mean TSH was statistically significant (p<0.05) between two groups.

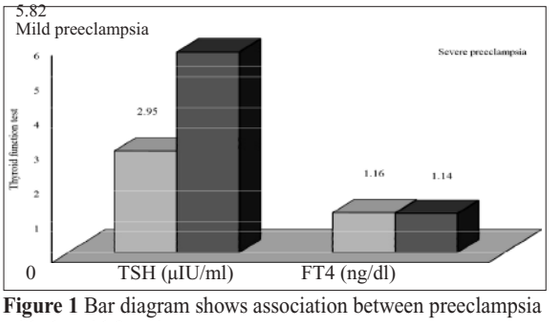

Figure 1 Bar diagram shows association between preeclampsia with thyroid function test

This bar chart shows mean TSH value in mild preeclampsia was 2.95μIU/ml whereas mean TSH value in severe preeclampsia was 5.8 which was nearly twice than mild preeclampsia. Mean FT_4 level in mild PE was 1.16 ng/dl whereas mean FT_4 in severe preeclampsia was 1.14 which was only slightly lower than mild preeclampsia.

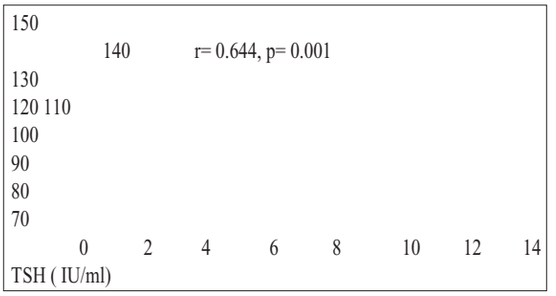

Figure 2 Correlation of diastolic blood pressure with TSH levels in PE cases (n=35)

Diastolic Blood Pressure (DBP) of 35 cases of preeclampsia were expressed as mm Hg TSH levels were measured by IU/ml. Pearson's correlation coefficient test was done. The value of Pearson's correlation coefficient was r=0.644 (p=0.001) which indicates significant positive correlation between TSH level and diastolic blood pressure.

Figure 2 Scatter diagram showing positive correlation (r=0.644, p=0.001) between TSH and diastolic blood pressure in preeclampsia group.

Discussion

The study shows in preeclampsia group 65.7% patients were nulliparous and 34.3% were multipara whereas in control group it was 62.9% and 37.1% respectively. The difference was not statistically significant (p>0.05) between two groups. So both the groups were matched for parity. In this study it was observed that Mean (±SD) of TSH was 4.8±3.1 μIU/ml in preeclampsia group and 2.2±1.1 μIU/ml in control group. The mean (±SD) of FT_4 was found 1.15±0.14 ng/dl in preeclampsia group and 1.23±0.21 ng/dl in control group. The mean TSH was significantly (p=0.001) higher in preeclampsia group but FT_4 was almost similar (p>0.05) in two groups. This observation is consistent with another study conducted by Kumar and colleagues, where the authors found the mean

(±SD) TSH of the study group and control group were 4.6±3.64 mIU/L and 2.5±2.01 mIU/L respectively and there was highly significant difference between the two groups ($p<0.001$).[18] The mean (±SD) FT_4 of 0.8 ± 0.44 ng/ml was in the study group and 0.9 ± 0.46 ng/ml was in the control group. The difference between the two groups was not statistically significant ($p>0.05$). Kharband colleagues also observed significant rise in TSH levels ($p<0.005$) in preeclampsia cases than normotensive pregnant controls thus their findings support our study.[19] In this series of observation, it was found that out of 35 pregnant women of each group 21(60.0%) women from preeclamptic study group and 10(28.6%) women from control group had abnormal TSH level (>3.5μIU/ml). So, 21(67.74%) women of total 31 pregnant women with abnormal TSH titers, had the diagnosis of preeclampsia whereas only 14 (28.57%) of the 49 pregnant women with normal TSH titers, had preeclampsia in third trimester. The difference between the two groups was found statistically significant ($p=0.008$, degree of freedom was 1). The odds ratio corresponding to TSH level >3.5 μIU/ml in the study group compared to the control group, was 3.8 which indicates pregnant women with abnormal TSH level (>3.5 μIU/ml) had 3.8 times more chance to develop preeclampsia than women with normal TSH level with 95% CI 1.2% to 11.6%.Kumar and colleagues also found statistically significant number of cases with PE having abnormally high level of TSH. In the study by Kumar and colleagues the odds ratio corresponding to TSH >5 mIU/ml in the study group compared to control group, was 4.85 (95% CI 2.19-10.74 [18]. Thus TSH was found to be a strong associating factor in the occurrence of preeclampsia.

In this study it was observed that, severe preeclampsia was predominant in the preeclampsia group, where 22(62.9%) patients were having severe preeclampsia and 13(37.1%) were having mild preeclampsia and it was observed that mean (±SD) of TSH was found 2.95±1.2 μIU/ml in mild preeclampsia and 5.82±3.43 μIU/ml in severe preeclampsia. The mean (±SD) of FT_4 was found 1.16±0.12 ng/dl in mild preeclampsia and 1.14±0.16 ng/dl in severe preeclampsia. The mean TSH level significantly ($p<0.05$) higher in severe preeclampsia but mean FT_4 was almost similar in both mild and severe preeclampsia. This indicates that there is a state of hypothyroidism that correlates with the severity of preeclampsia. Kharb and colleaguesfound significantly ($p=0.001$) higher TSH value in severe preeclampsia (5.63±2.37μIU/mL) as compared with mild preeclampsia (3.42±1.61μIU/mL) which is consistent with the current study.[19] In this present study it was observed that out of total 21 cases with TSH level >3.5 IU/ml, 16 (76.2%) had systolic blood pressure ≥160 mmHg and 5(23.8%) had systolic blood pressure in the range of 140-<160mm Hg. Out of 14 cases with TSH level ≤3.5 IU/ml 6(42%) had systolic blood pressure ≥160 mmHg and 8(57.1%) had systolic blood pressure in the range of 140-160 mmHg. Again out of 21 cases with TSH level >3.5 IU/ml, 15(71.4%) patients had diastolic blood pressure ≥110 mmHg and 6(28.6%) had diastolic blood pressure in the range of 90-<110mmHg. Out of 14 cases with TSH level ≤3.5 IU/ml 5(35.71%) had diastolic blood pressure ≥160 mmHg and 9(64.28%) had diastolic blood pressure in the range of 90-<110 mmHg. The difference was statistically significant ($p<0.05$) among the two groups. So it was observed that high systolic blood pressure and diastolic blood pressure were associated with higher level of serum TSH. Similarly, Study conducted by Kharb and colleagues also observed TSH level increases significantly with increase in mean arterial pressure.[19]

In this present study significant positive correlation was found between TSH level with systolic blood pressure, diastolic blood pressure and proteinuria in preeclampsia group where the values of Pearson's correlation coefficient were $r=0.550$, ($p=0.001$), $r=0.644$, ($p=0.001$) and 0.618, $p= 0.001$ respectively.

Limitation

The present study was conducted within a short period of time. The study population was selected from one selected hospital, so that the results of the study may not be reflect the exact picture of the country. Small sample size with purposive sampling was also a limitation of the present study. The study was not based on longitudinal observation but was conducted as a cross-sectional design without baseline thyroid function status in

the first trimester before development of preeclampsia and without follow-up data after delivery limits the ability of the study to confirm that TSH plays a distinctly causative role in preeclampsia.

Conclusion

The study showed that serum TSH level significantly increases in preeclampsia in comparison to normal pregnancy and it also found significantly high in severe preeclampsia than mild preeclampsia without concomitant changes in FT_4 level. So it can be concluded as abnormal TSH titer may be associated with risk of occurrence of preeclampsia and its severity. Therefore, identification of thyroid function abnormalities in pregnancy and appropriate measures to correct them might be of help in predicting the occurrence and severity of preeclampsia

Recommendation

Further longitudinal studies with larger sample size with multicentric approach and long durationare required to establish the actual relationship of abnormal thyroid function with preeclampsia. This will strengthen the outcome of this study result.

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Contribution of authors

LK-Conception, acquisition of data, data analysis, drafting & final approval.
SMMH-Acquisition of data, data analysis, drafting & final approval.
NH-Design, acquisition data, critical revision & final approval.
NH-Interpretation of data, critical revision & final approval.
SS-Data analysis, critical revision & final approval.
NR-Interpretation of data, critical revision & final approval.
FY-Acquisition of data, drafting & final approval.
DKM-Data analysis, critical revision & final approval.

Disclosure

All the authors declared no competing interest.

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