Association of Thyroid Stimulating Hormone with Thyroid Peroxidase Antibody in Apparently Healthy Pregnant Women

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Abstract

Background: Undiagnosed thyroid disorders have different maternal and fetal adverse outcome. Euthyroid pregnant women with thyroid peroxidase antibody could silently go to overt hypothyroidism, but these can be prevented by identifying the patient with positive thyroid peroxidase antibodies in their early gestation. Objective of the study is to determine the association of serum thyroid stimulating hormone with thyroid peroxidase antibody in apparently healthy pregnant women.

Materials and methods: This cross-sectional study was carried out in the Department of Obstetrics and Gynecology, BSMMU between Ist March 2016 and 28th February 2017. A total of 245 apparently healthy pregnant women were included in this study. These subjects were tested for Thyroid Peroxidase Antibody (TPO-Ab) serum Thyroid Stimulating Hormone (TSH) and serum Free Thyroxine (FT4).

Results: 71(29%) of women at first trimester were found to have TSH > 2.5 and TPO-Ab positive in 54 (22%). Out of these positive subjects 22(30.98%) have raised TSH (>2.5 mIU/L). FT4 was low in 7(3%) of all subjects.

Conclusion: There is a remarkable correlation between TSH and TPO-Ab ($p < 0.05$) in first trimester of pregnancy. Thus TPO-Ab could be considered as a screening tool.

Key words: Pregnancy; Thyroid peroxidase antibody; Thyroid stimulating hormone.

Introduction

Pregnancy results in profound anatomical, physiological, endocrine and immunological changes. These include significant changes of the maternal thyroid gland.[1] Hypothyroidism is the second most common endocrinopathy during pregnancy and its incidence range from 2% to 5%.[2] Thyroid Peroxidase Antibodies (TPO-Ab) are self-developed antibodies that target the membrane-associated hem glycoprotein, thyroid peroxidase of the thyroid cells. They are symbol of thyroid autoimmunity. In patients with subclinical hypothyroidism, the nding of TPO antibodies confers an increased risk of progression to overt hypothyroidism.[3] Subclinical thyroid disease is a laboratory diagnosis where patients have no signs and symptoms. Only 20–30% of women with overt hypothyroidism have symptoms associated with low thyroid hormone levels and complaints of fatigue and weight gain may often mimics to the pregnancy itself.[4]The gland increases 10% in size during pregnancy in iodine-replete countries and by 20% – 40% in areas of iodine deficiency.[5] In the first trimester of pregnancy there is a transient rise of FT4 due to elevated level of Human Chorionic Gonadotropin (HCG) in the circulation and there is a decrease of FT_4 in the second and third trimester of pregnancy.[6] HCG, a glycoprotein hormone secreted by placenta has two subunits – alpha and beta. Alpha subunit is similar to TSH but the beta subunit is unique and specific. In about 0.3% of pregnancies, gestational transient hypothyroxinemia is seen due to a molecular variant of HCG which acts as a TSH agonist and thus cause rise in level of FT4.[7] Thyroid Peroxidase Antibody (TPO-Ab) is a serological marker of autoimmune thyroid disease.[8] Thyroid peroxidase antibody (TPO-Ab)

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positive rate in early pregnancy ranges from 5% to 17%.[9] The presence of TPO antibodies are associated with devastating outcomes, including miscarriage, preterm delivery, subfertility, perinatal mortality, large for gestational age, low birth weight infants and post-partum thyroiditis.[3] The chance of developing post-partum thyroiditis is 30-52%.[10] In early pregnancy high TSH and thyroid autoimmunity is associated with 4 fold increase risk for gestational diabetes. Women positive for thyroid antibodies without elevated TSH levels in early pregnancy have higher risk for spontaneous preterm delivery.[11] Adequate concentrations of T4 are essential for neural development and this T4 can only be maternally derived.[7] Increase incidence of mental retardation is observed as a result of hypothyroidism of mother or fetus.[12] High TSH and TPO-Ab positive in early pregnancy is associated with 3 fold increased risk for low birth weight neonates.[11] This study was carried out to see the association of TPO-Ab with TSH in apparently healthy pregnant women. The results may be helpful in early prediction and prevention of serious consequences of thyroid diseases during pregnancy, post-partum thyroiditis and also its consequences on fetus.

Materials and methods

This cross-sectional study was carried out in the Department of Obstetrics and Gynecology, BSMMU, Dhaka between Ist March 2016 and 28th February 2017. Ethical clearance for the study was taken from the institutional review board, BSMMU. Permission for the study was taken from the concerned departments where this study was conducted. A total of 245 singleton pregnant women attending outpatient antenatal clinic at their first trimester with no previous history of systemic disease, non-immunosuppressive, without any history of autoimmune disease and with no known thyroid disease diagnosed before pregnancy were enrolled for the 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 obtained. An interviewer administered questionnaire was used for data collection. Detailed socio-demographic data and other relevant history was recorded. Then physical examination and obstetric examination was done with due consent. Pregnancy was confirmed with USG. It was followed by the investigation of serum TSH, FT_4 and TPO-Ab. Investigation reports were noted and the association of TPO antibody was calculated with TSH. With all aseptic precaution required blood sample was collected from the median antecubital vein from all study subjects. Collected blood was allowed to clot and the centrifuged. Separated serum was collected into plastic micro centrifugated tubes and appropriately labeled which was used for estimation of thyroid peroxidase antibody and serum FT_4 & TSH. The reference value of TPO-Ab level: > 12 IU/ml considered as raised.[13] The reference value for TSH according to current ATA guideline, trimester specific during pregnancy is strongly recommended (Level I). According to it, the first trimester reference range is 0.1-2.5 mIU/L.[5] Thus > 2.5 mIU/L was considered raised. Result of FT_4 assay is method specific and trimester specific reference range is required. But there is no universally accepted trimester specific reference range available so method specific reference range for general population supplied by the manufacture is used which is 9.14-23.81 pmol/L. <9.14 pmol/L was considered low. Statistical analyses of the results were obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS 24).

Results

Table I Distribution of patients by their demographic characteristics (n=245)

Demographic characteristics	Frequency	Percentage (%)
Age* (In years)		
≤ 20	37	15.1
21 – 25	72	29.4
26 – 30	102	41.6
> 30	34	13.9
Educational status		
Illiterate	9	3.7
Primary	56	22.9
Secondary	57	23.3
Higher Secondary	90	36.7
Graduate or above	33	13.5
Occupation		
Student	17	6.9
Housewife	176	71.8
Service Holder	52	21.2
Family income		
< 10,000	86	35.1
10,000 – 25,000	112	45.7
25,000 – 50,000	29	11.8
> 50,000	18	7.3

*Mean Age: 26.34 ± 2.54, Age Range: 16 – 41 years.

Table I shows majority of the patients were in the age group 21-30 years. Mean age was 26.34±2.54 ranging from 16 to 41 years. Maximum patients had educational status of secondary and higher secondary group (23.3%, 36.7% respectively) (71.8%) were housewife and 21.2% were service holder.

Table II Distribution of patients by their obstetric history (n=245)

Parameters	Frequency	Percentage (%)
Gravida		
Primigravida	112	45.7
Multigravida	133	54.3

Table II shows that among all subjects Primigravida were 112 (45.7%) and Multigravida were 133 (54.3%).

Table III Distribution of patients by their thyroid profile (n=245)

Parameter		n (%)	Mean±SD	Total (n=245)
TSH (mIU/L)	Normal (0.1-2.5)	174 (71)	1.41±0.68	2.79±2.37
	High (>2.5)	71 (29)	6.16±1.48	
FT_4 (pmol/L)	Normal (9.14-23.81)	238 (97)	16.87±3.89	16.55±4.28
	Low (< 9.14)	7 (3)	5.55±1.92	
TPO-Ab(IU/ml)	Negative (< 12)	191 (78)	4.60±3.09	32.89±70.60
	Positive (> 12)	54 (22)	132.98±99.10	

Table III shows that out of 245 subjects 71 (29%) had high TSH (> 2.5 mIU/L) and rest 174 (71%) had TSH within normal range.

Subjects with normal TSH were 174 (71%) with mean of 1.41±0.68 and high TSH (> 2.5 mIU/L) were in 71 (29%) with mean of 6.16±1.48. Mean of TSH among 245 subjects were 2.79±2.37. FT4 within normal range among 245 subjects were 238 (97%) with mean of 16.87±3.89 and low 7 (3%) with mean 5.55±1.92. Mean of FT4 of 245 subjects were 16.55±4.28. Mean TPO-Ab of 245 subjects were 32.89±70.60 among them positive were 54 (22%) and 191(78%) negative with mean of 132.98±99.10 and 4.60±3.09 respectively.

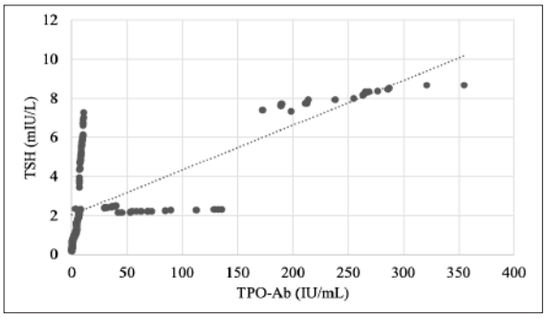

Figure 1 Correlation of serum TSH with serum TPO-Ab

Figure 1 shows a scatter diagram where linear positive correlation between serum TSH and TPO-Ab in the study subjects were shown.

Table IV Relationship between TPO-Ab and TSH (n=245)

TPO-Ab	TSH					p-value
	High		Normal			
	n=71	%	n=174	%	χ^2	
Positive	22	31%	32	18.4%	4.655	0.031^s
Negative	49	69%	142	81.6%		

s = significant.

p value reached from Pearson's Chi Square test

Table IV shows the relationship between the TPO-Ab, positive and negative and TSH, high and normal. There was statistically positive correlation between sub groups (p=0.031).

Table V Relationship between TPO-Ab and FT_4 (n=245)

TPO-Ab	FT_4					p-value
	Low		Normal			
	n=7	%	n=238	%	χ^2	
Positive	3	42.85%	51	21.42%	1.817	0.178^{ns}
Negative	4	57.14%	187	78.57%		

ns = non-significant.
p value reached from Pearson's Chi Square test.

Table V explains the relationship between subgroups of TPO-Ab (positive and negative) and FT_4 (Low and Normal). There was negative correlation between them (p=0.178)

Discussion

Pregnancy has extensive effects on balancing thyroid function in healthy women. Many studies have shown that 5-22% of pregnant women have thyroid auto antibody (TPO-Ab) and 2 – 3% of them have undiagnosed hypothyroidism which may adversely affect both mother and the fetus.[14] In this study serum TSH, serum FT4 and TPO-Ab were measured. A total of 245 pregnant women were evaluated and among them 15.1% were under 20 years of age, 29.4% between 21 to 25 years of age, 41.6% were between 26-30 years of age and more than 30 years of age were 13.9%. The age range of patients was between 16 and 41 years with the mean age of 26.23±4.93. Majority of them were between 26 to 30 years of age. Out of all respondents, 3.7% were illiterate, 22.9% were studied primary level, 23.3% upto secondary

level, 36.7% upto higher secondary level and graduate or above were 13.5%.In current study, maximum patients were housewife 176(71.8%), 17(6.9%) being students and 52(21.2%) service holder. Majority of lower and middle class family. The present study shows that out of all pregnant women 112(45.7%) were primi gravida, 133(54.3%) were multigravida, more seen in parous women. Similar results are also observed by studies conducted by Karakosta and colleagues and Abbassi-Ghanavati and colleagues.[11,21] Based on a number of studies, Positive Thyroid Antibodies (TPO-Ab) are believed to be a significant risk factor for hypothyroidism in pregnancy and postpartum period.[16] This present study also highlights the fact of association of thyroid stimulating hormone with TPO-Ab. A total of 71 (29%) pregnant women had TSH • 2.5 mIU/L 71% with normal TSH and mean TSH of 2.79±2.37mIU/L which was consistent with the study of Nahar and colleagues, where their study shows prevalence of 30% with the mean 2.12±1.68 mIU/L.[15] Present study found that TPO-Ab was elevated in 54 (22%) of all pregnant women. The study conducted by Dhanwal and colleagues had shown the prevalence of TPO-Ab positive in 18.07%, which was similar to the present study.[17] The finding is also supported by the study conducted by Nahar and colleagues.[15] 22 (30.98%) among 71 patients with high TSH were found to be TPO-Ab positive in this study. The study done by Rajput found 39.4% among high TSH (hypothyroidism) were positive for TPO-Ab.[18] The prevalence of this study was in support of the current study. Low Free Thyroxine (FT4) concentration in early pregnancy is an important risk factor for the impaired development of infant. Particularly at risk are the mothers with low FT4 and high antibody titers. The diagnosis of hypothyroidism is based on low level of free thyroxine and elevated level of TSH.[19] In the present study, out of 245 pregnant women 7 (3%) subjects showed low and 238 (97%) had normal FT_4 level, and mean was 16.55±4.28 pmol/L. None of the patient had isolated hypothyroxinemia (Low FT4 and normal TSH). Infect, subclinical hypothyroidism (Low FT4 and high TSH) accounts for 9.86% of all subjects. The study conducted by Springer and colleagues reveal out of 2937 pregnant women without any risk factors for thyroid disorders found 7.8% of hypothyroid women, which is similar to the present study.[20] In present study 54 (22%) of all pregnant women were found to be positive for TPO-Ab, out of these 22 (40.7%) had TSH more than 2.5 and 32 (59.2%) had normal TSH with a significant p value among both the groups reached by pearson's chi square of • 0.05. Study conducted by Nahar and colleagues showed 21.5% of positive TPO-Ab and out of which 37.2% had raised TSH and 62.7% had normal TSH with significantly positive correlation between TSH and TPO-Ab.[15] Karakosta, Abbassi-Ghanavati and Bhattacharyya shows similar results.[11,21,22] These studies also shows positive TPO-Ab in patients with high TSH but significant number of women in their first trimester had TPO-Ab positive with normal TSH. These patients were more likely to have adverse pregnancy outcome. Another study conducted by Meena shows the same.[23] A similar study done by Lin, Zhang and Long and colleagues where analysis of thyroid peroxidase antibody in early pregnancy on 611 cases showed 22.9% with positive TPO-Ab and among them significant number of TPO-Ab positive cases were also present in euthyroid women, also TPO-Ab and TSH were positively correlated and that FT_4 had negative correlation.[24] Dhanwal and colleagues also shows the same.[17] Above studies also show positive correlation between TPO-Ab and TSH along with adverse pregnancy outcome in TPO-Ab positive group in euthyroid women and more when combined with higher TSH.

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 The study was not based on longitudinal observation but was conducted as a cross-sectional design and without follow-up data after delivery limits the ability of the study to that TSH and TPO-Ab plays a distinctly causative role in maternal and fetal morbidity. Small sample size with purposive sampling was also a limitation of the present study.

Conclusion

This study concluded that significantly evident TPO-Ab is found positive more in pregnant women with raised TSH level. in apparently healthy pregnant women without concomitant changes in FT_4 level. There was a positive correlation between TSH and TPO-Ab positive subjects among the pregnant women.

Recommendation

Further longitudinal studies with larger sample size with multicentric approach and long duration are needed to establish the actual relationship of of thyroid stimulating hormone and thyroid peroxidase antibody in apparently healthy pregnant women. This will strengthen the outcome of this study result.

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Contribution of authors

NR-Conception, design, data collection, data analysis, interpretation of results, draft manuscript & final approval.

KN-Data analysis, interpretation of results, manuscript preparation & final approval.

NH-Acquisition of data, critical revision & final approval.

NH-Acquisition of data, critical revision & final approval.

LK-Data collection, data analysis, interpretation of results, draft manuscript & final approval.

DKM-Data collection, data analysis, drafting & final approval.

MTS-Data collection, data analysis, drafting & final approval.

FBK-Data collection, data analysis, drafting & final approval.

YD-Data analysis, critical revision & final approval.

Disclosure

All the authors declared no competing interests.

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