**Original article**

# Assessment of Thyroid Peroxidase Antibody And Thyroid Stimulating Hormone In First Trimester Of Pregnancy

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**Abstract**

***Introduction:*** Maternal thyroid dysfunction during pregnancy has been associated with a number of adverse outcomes, like preterm birth, placental abruption, foetal death and impaired neurological development in the child. Simultaneously the presence of antibody to thyroid peroxidase results miscarriage, preterm birth and maternal post partum thyroid disease. Post partum thyroiditis is closely associated with the presence of antibodies to thyroid peroxidase (TPO). Indeed if a pregnant woman is positive for TPO antibodies early in pregnancy, her chances of developing post partum thyroiditis is 30-52%. ***Objective:*** To find out the level of TPO-Ab and thyroid status in first trimester of pregnancy. ***Method:*** The cross sectional study was designed in Department of Biochemistry, BSMMU, Dhaka. Following inclusion and exclusion criteria 200 sample was selected by purposive and convenient sampling. The study parameters were- thyroid peroxidase antibody (TPO-Ab); serum thyroid stimulating hormone (TSH); serum free thyroxin ($FT_4$). ***Results:*** 43 (21.5%) pregnant women of first trimester was found to be TPO-Ab positive, among these 43 subjects 16 (8.0%) had raised TSH i.e. >2.5 mIU/L and 27 had TSH level <2.5 mIU/L. Low serum $FT_4$ was in 9 (4.5%) subjects. The study revealed that, there was a significant positive correlation between positive TPO-Ab (>12 IU/mL) and serum TSH level of study subjects and there was negative correlation between serum TSH (>2.5 mIU/L) and serum $FT_4$ in study subjects. ***Conclusion:*** TPO-Ab positivity in first trimester of pregnancy and TPO-Ab positivity was associated with higher TSH and low $FT_4$ level.

**Key Word:** Thyroid Peroxidase Antibody, Thyroid Status, Pregnancy.

## Introduction

Pregnancy results a series of profound physiologic changes that have a significant effect on maternal thyroid function. Autoimmune thyroid disorders are associated with autoantibodies directed against thyroglobulin and thyroid peroxidase (anti-TPO). Anti-TPO occurs in 10% of pregnant women, half of whom reportedly develop postpartum thyroid dysfunction[1]. Maternal thyroid dysfunction during pregnancy has been associated with a number of adverse outcomes. For example, elevated maternal thyroid stimulated hormone (TSH) has been associated with an increased risk of preterm birth, placental abruption, foetal death and impaired neurological development in the child. Similarly the presence of antibody to thyroid peroxidase has been associated with increased risk of miscarriage, preterm birth and maternal post partum thyroid disease[2]. Gestational hyperthyroidism is associated with increased risk of several adverse outcomes, including preeclampisa, premature labor, fetal or perinatal death and low birth weight. Hyroidism usually is the result of Grave's disease, which involves development of autoantibodies against the TSH receptor that stimulate the thyroid gland. Proper maternal thyroid function during pregnancy is important for the health of both the mother and developing child. Measurement of serum thyroid stimulating hormone (TSH) and thyroid peroxidase antibodies (TPO-Ab) are two common ways to assess maternal thyroid status[3]. Thyroid hormones are critical for development of the fetal and neonatal brain, as well as for many other aspects of pregnancy and

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fetal growth. Hypothyroidism in either the mother or fetus frequently results in fetal disease; this includes a high incidence of mental retardation[4].

TPO antibodies, are also known as Antithyroid Peroxidase Antibodies. (In the past, these antibodies were referred to as Antithyroid Microsomal Antibodies or Antimicrosomal Antibodies and a major autoantigen in autoimmune thyroid diseases. Measuring TPO antibodies in euthyroid subjects can be used to identify subjects with increased risk of hypothyroidism[5]. TPO is a key enzyme is the formation of thyroid hormone and TPO is an enzyme which is responsible for the oxidation of iodide and binding of iodine to tyrosyl residue of thyroglobulin (organification) then iodotyrosine residues undergo coupling process[6]. Post partum thyroiditis is closely associated with the presence of antibodies to thyroid peroxidase (TPO). Indeed if a pregnant women is positive for TPO antibodies early in pregnancy, her chances of developing post partum thyroiditis is 30-52%[7].

Many studies has been done on the relationship between existing thyroid autoimmunity and the probability of spontaneous abortion. Stagnaro-Green et al. found that the presence of TPO and / or thyroglobulin antibodies in the first trimester of pregnancy is a risk factor for spontaneous foetal loss. They found that the spontaneous abortion rate in thyroid antibody positive women was significantly higher than in antibody negative women[7]. Around 10% of women over 20 years of age have elevated concentration of thyroid peroxidase antibodies, and early sign of thyroid autoimmunity and a major risk factor for the development of over thyroid dysfunction, both during the postpartum period and in general. The presence of thyroid TPO-Abs during gestation is associated with the occurrence of subsequent depression during the postpartum period and as such can be regarded as a marker for depression[8].

These antibodies work against thyroid peroxidase, an enzyme that plays a part in the T4-to-T3 conversion and synthesis process. TPO antibodies can be evidence of tissue destruction, such as Hashimoto's disease, less commonly, in other forms of thyroiditis such as post-partum thyroiditis. Thyroid peroxidase antibodies are present in 10% of women at 14 weeks of gestation and are associated with an increase rate of pregnancy failure and increased incidence of gestational thyroid dysfunction, a predisposition to postpartum thyroiditis. Hypothyroidism (including subclinical hypothyroidism) occurs in 2.5% of pregnant women due to autoimmune thyroiditis. Immunological factors may play an important role in the reproductive processes of fertilization, implantation and placental development. Women have a high degree of immunological responsiveness which is reflected by their increased susceptibility to non organ specific and organ specific autoimmune. Such increased susceptibility is supported by the fact that thyroid auto-antibodies have been associated with an increased risk for pregnancy loss. It has also been reported that 5-10% of postpartum women demonstrate evidence of thyroid dysfunction. Recent studies have suggested an association between autoimmune factors and reproductive wastage[9].

Although gestational hyperthyroidism is uncommon (0.2%), hypothyroidism (auto-immune disease or suboptimal iodine intake) occurs in 2.5% of women and is predictive of reduced neonatal and child neuropshychological development and maternal obstetric complications. Post partum thyroid dysfunction (PPTD) occurs in 5-10% in women and is associated with antithyroid peroxidase antibodies (anti TPO-Ab) in 10% of women in early pregnancy. Therefore, screening for thyroid dysfunction in pregnancy should be considered. PPTD can be predicted by measurement of anti TPO-Ab in early gestation[10]. To assess the prevalence, incidence, and risk factors for thyroid dysfunction during and after pregnancy in women with diabetes mellitus type 1 (DM type-I) Gallasmeasured TSH, Free $T_3$, and TPO-Ab in pre-pregnancy first and last trimester of pregnancy, and at 1.5, 3, 6, 9, and 12 months after delivery and found Prevalence of PPTD in women with DM type-II. The prevalence of overt PPTD in women with DM type-I was > 3-fold higher than the general population[11].

Autoimmune thyroid disease shows impairment of thyroid function during gestation and seems to suffer from higher rate of obstetrical complications. As there is alteration of thyroid function in pregnancy it is necessary to diagnose this alteration and to monitor thyroid function during pregnancy. Women with increased level of TPO-Ab during pregnancy are associated with postpartum depressive illness and increased risk for impaired devel-

opment of their offspring[8]. There is paucity of information regarding the thyroid function and TPO-Ab status is early pregnancy in our country. TPO-Abs testing may be a routine diagnostic tool which can helps the obstetricians to identify women at risk for depression and also prevent premature birth, foetal loss, and congenital malformation. So implementation of routine screening for TPO-Ab in early pregnancy is very important to prevent the adverse outcome of pregnancy. The reference interval of TSH during the first trimester of pregnancy differs substantially from that for non-pregnant women, and applying the general laboratory reference range to pregnant women results in misclassification of thyroid status for 20.5% of women. Pathology laboratories of Bangladesh should adopt pregnancy-specific reference intervals for thyroid function tests[12].

**Objective of the study**

To find out the level of TPO-Ab and thyroid status in first trimester of pregnancy.

**Specific Objectives**

Estimation of the maternal serum TPO-Ab in first trimester of pregnancy.

Estimation of the maternal serum $FT_4$ and TSH in first trimester of pregnancy.

Correlation of maternal serum $FT_4$, TSH with TPO-Ab in first trimester of pregnancy.

**Methods**

This cross sectional study was conducted in the Department of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh for a period of one year commencing from January 2008. 200 normal uncomplicated pregnant women of first trimester were taken purposively and conveniently. This study was carried out among the subjects who were non smoker, non alcoholic, with no systemic diseases, no immunosuppressive therapy and with no previous treatment for thyroid diseases. After confirmation of pregnancy by ultrasound they were examined thoroughly and the relevant data (e.g. anthropometric measurement, dietary habit, personal habit, obstetrical history were collected). Base line laboratory investigations (Hb%, Urine R/E, serum ALT & ALP, Glucose, Urea and Creatinine concentration) were done to exclude diabetes mellitus, liver disease and renal disease. The participants were thoroughly briefed about the nature and purpose of the study. Their participation was voluntarily and they agreed to keep in touch with us. Patient's residence address and telephone numbers were kept in record. During first trimester of pregnancy blood were collected to estimated thyroid peroxidase antibody and TSH.

The research protocol was approved by Ethics Committee of BSMMMU.

***Laboratory methods:*** From all the study subjects required blood sample was collected from the median antecubital vein by disposable plastic syringe with all aseptic precautions. Blood was transferred immediately into a dry clean plastic test tube with a gentle push to avoid hemolysis. Collected blood was allowed to clot and then centrifuged. Separated serum was collected into plastic micro centrifuged tubes and appropriately labeled, which was used for estimation of serum peroxidase antibody and serum (TSH) concentration.

***Study parameters:***Parameters below were analyzed in all study subjects-

Thyroid peroxidase antibody (TPO-Ab) done by Microparticle Enzyme Immunoassay Method (Abbott-AxSym)[12].

Serum Thyroid stimulating hormone (TSH) done by Microparticle Enzyme Immunoassay Method (Abbott-AxSym)[13].

**Operational Reference range:**

TPO-Ab level : $>12$ IU/mL considered as positive[3]

High TSH : $>2.5$ mLU/L (considered as abnormal)[14]

***Statistical Analysis:***All data were recorded systematically in a preformed data sheet. Statistical analysis was performed by using SPSS for windows version 12.0 Chi-square test, proportion test (Z test) and Spearman's correlation coefficient test and Mann Whitney U test were done as test of significance. 95% confidence limit ($p<0.05$) was taken as level of significance.

**Results and Observations**

200 normal uncomplicated pregnant women of first trimester were taken to evaluate the thyroid peroxidase antibody and thyroid hormone status in the first trimester of pregnancy. Thyroid peroxidase antibody (TPO-Ab) and TSH were measured in all study subjects. The results were expressed as mean $\pm$ SD. Serum concentrations of TPO-Ab was expressed in IU/mL and TSH in mIU/L.

Table I shows age distribution of study subjects. The mean ± SD age of the study subjects were 24.20 ± 4.82 years.

**Table I : Age distribution of the study subjects.**

| Age in years | Total Number | Mean age (years) mean ± SD |
|---|---|---|
| 16-40 | 200 | 24.2 ± 4.82 |

Table II shows distribution of TPO-Ab in study subjects. Out of 200 pregnant women 43 (21.5%) had TPO-Ab positivity (considering cut off value more than 12 IU/mL as positive).

**Table II: Distribution of TPO-Ab in study subjects.**

| Parameter | Positive | Percent | Negative | Percent | Cut off value |
|---|---|---|---|---|---|
| TPO-Ab | 43 | 21.5% | 157 | 78.5% | >12 IU/mL |

Table III shows thyroid hormone (TSH) status of the study subjects. Mean ± SD of serum TSH were 2.12 ± 1.68 mIU/L.

**Table III : Thyroid hormone status of the study subjects.**

| Parameter | Mean ± SD |
|---|---|
| TSH mIU/L (n=200) | 2.12 ± 1.68 |

Table IV shows distribution and comparison of study subjects on the basis of TSH reference range in first trimester of pregnancy. Out of 200 pregnant women 60 (30.0%) had TSH >2.5 mIU/L and 140 (70.0%) had TSH < 2.5 mIU/L. Mean ± SD of serum TSH of the subject having > 2.5 mIU/L were 3.76 ± 2.18 mIU/L and serum TSH < 2.5 mIU/L were 1.42 ± 0.63 mIU/L. The difference between TSH >2.5 mIU/L and TSH < 2.5 mIU/L was statistically significant.

**Table IV: Distribution and comparison of study subjects on the basis of TSH reference range in first trimester of pregnancy.**

| Parameter TSH | Number N=200 | Percentage | Mean ± SD | Z | p value |
|---|---|---|---|---|---|
| TSH >2.5 mIU/L | 6 | 30% | 3.76 ± 2.18 | 8.35 | <0.001 |
| TSH <2.5 mIU/L | 140 | 70% | 1.42 ± 0.63 | | |

p value reached by Z test and p <0.05 taken as level of significance. (Cut off value 2.5 mIU/L)

Table V shows distribution and comparison of TPO-Ab in study subjects. Median (range) of serum TPO-Ab level in positive and negative subjects were 16.8 IU/mL (12-1000 IU/mL) and 3.9 IU/mL (0.0-11.70 IU/mL) respectively. There was a statistically significant difference between TPO-Ab positive and TPO-Ab negative pregnant women of first trimester.

**Table V: Distribution of the study subjects on the basis of TPO-Ab in study subjects.**

| Parameter | TPO-Ab Positive (≥12 IU/mL) n=43 Median (range) | TPO-Ab Negative (<12 IU/mL) n=157 Median (range) | Mann Whitney U value | p value |
|---|---|---|---|---|
| TPO-Ab (IU/mL) | 16.8 IU/mL (12-1000 IU/mL) | 3.9 IU/mL (0.0-11.70 IU/mL) | 3006 | <0.05 |

p value reached by Mann Whitney U test and p<0.05 taken as level of significance.

Table VI shows correlation analysis of serum positive TPO-Ab level (>12 IU/mL) of study subjects with their serum TSH concentration. A significant positive correlation (r = 0.466, p<0.01) was observed between positive TPO-Ab level and TSH i.e. serum TPO-Ab level increase with increase of serum TSH level.

**Table-VI: Correlation of serum TPO-Ab (>12 IU/mL) level with serum TSH of study subjects.**

| Dependent / Independent | r value | p value |
|---|---|---|
| Positive TPO-Ab / TSH | 0.466 | <0.01 |

p value reached by spearman s rho correlation test and p<0.05 taken as level of significance.

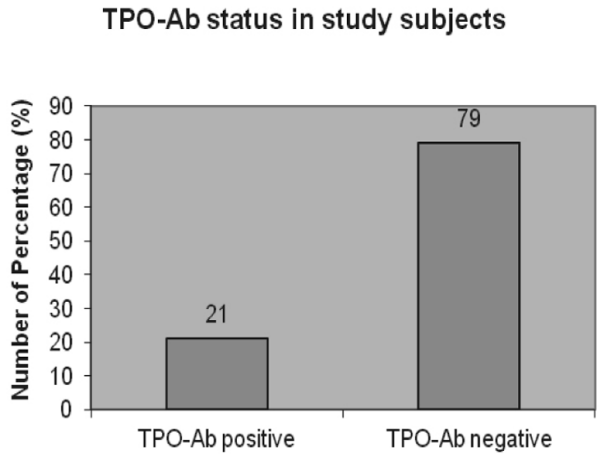


**Fig. 1:** TPO-Ab status in study subjects.

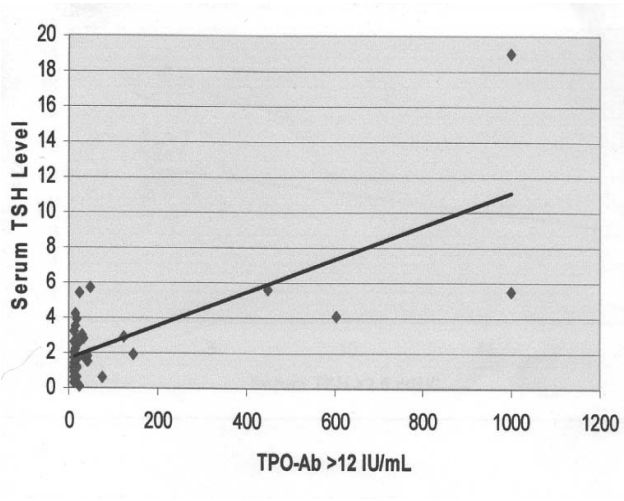


**Fig. 2:** Correlation of serum TPO-Ab (>12 IU/L) with serum TSH concentration in study subjects.

## Discussion

Maternal TPO-Ab positive during pregnancy is associated with post partum depressive symptom and impaired child development and also related with increased miscarriage, premature birth, low birth weight, congenital malformation and perinatal death. Thyroid hormones are critical for development of the fetal and neonatal brain, as well as for many other aspects of pregnancy and fetal growth. Hypothyroidism in either the mother or fetus frequently results in fetal disease; this includes a high incidence of mental retardation. Pregnancy has profound effects on the regulation of thyroid function in healthy women. Many studies have shown that 5-22% of pregnant women have TPO-Ab, 2-3% of them have undiagnosed hypothyroidism and it may adversely affect both mother and their foetus[15].

In this study to find out the increased level of TPO-Ab and to evaluate the thyroid status in pregnant women of first trimester, we have measured serum TPO-Ab, serum TSH and serum $FT_4$ level in 200 pregnant women. TPO-Ab reference range (>12 IU/mL) is considered abnormal i.e. positive[3]. Our study revealed that out of 200 pregnant women, 43 (21.5%) had elevated serum TPO-Ab. Pearce et al. found 12.4% elevated TPO-Ab and Stricker et al. found 19.4% elevated TPO-Ab. In another study out of 487 pregnant women raised TPO-Ab was found in 106 patients (22.0%)[2,8,18]. These findings are consistent with our observation. Post partum thyroiditis is closely associated with the presence of antibody to thyroid peroxidase. Indeed if a pregnant women is positive for TPO-Ab early in pregnancy her chances of developing postpartum thyroiditis is 30-52%[7]. It has been suggested that an upper normal limit for TSH in pregnant women of first trimester is 2.5 mIU/L, compared with 4.0 to 4.5 mIU/L in non pregnant women[14].

High serum TSH and TPO-Ab positivity were the most common in the first trimester of pregnancy in 5.7% and 13.8% respectively. Pregnant women with antoimmune thyroid disease may undergo serum TPO-Ab test because antibodies are able to cross the placenta and cause hypothyroidism[16]. In our study raised serum TSH (>2.5 mIU/L) and TPO-Ab were observed in 60 (30.0%) and 43 (21.5%) subjects respectively. This result is well supported by the study of Quinn[3].

Our study showed TPO-Ab positivity in 43 (21.5%) study subjects, among them raised serum TSH (>2.5 mIU/L) was in 16 (8.0%) and serum low $FT_4$ was in 6 (3.0%). These subjects are particularly at-risk for hypothyroidism. Maternal complications of untreated hypothyroidism include microcytic anaemia, preeclamsia, placental abruption, post partumhaemorrhage and miscarriage. Foetal or neonatal complications include prematurity, low birth weight, congenital anomalies, stillbirth and poor neuropsychological development[17-19].

In our study significant positive correlation ($r=0.738$, $p<0.01$) was observed between serum positive TPO-Ab level and TSH, indicate that serum TPO-Ab level increases with increase of serum TSH level. Our study was well in agreement with the Pearce et al. in 2008, who found that ele-

vated serum TPO-Ab levels are associated with higher TSH and lower $FT_4$ values[20].

**Conclusion**

This study do suggests that TPO-Ab could be regarded as a marker for the occurrence of future depression at risk group of patients. Complications associated with TPO-Ab positivity and altered thyroid function in first trimester of pregnancy are post partum thyroiditis, maternal depression and permanent hypothyroidism occurs in as many as 30% of pregnant women. These patients are also at high risk for recurrent PPT with subsequent pregnancies. So our recommendation is to reveal the relationship between postpartum thyroid dysfunction and thyroid antibody (TPO-Ab), because the presence of TPO-Ab has been reported as the most prominent risk factor for developing postpartum thyroid dysfunction and impaired child development. So we recommend the implementation of routine screening for TPO-Ab in first trimester of pregnancy.

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