|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
*Index Copernicus Value 2018: 75.71*
Original Research Article
Volume 4, Issue 7; July: 2020; Page No. 49-53

# SIGNIFICANT ASSOCIATION BETWEEN ANTI-THYROID PEROXIDASE (ANTI-TPO) ANTIBODIES AND LOW BIRTH WEIGHT IN EUTHYROID PREGNANT WOMEN

**Dr. Bhanwar Singh Meena[1], Dr. Harendra Kumar Netra[2], Dr. Amit Kumar Joshi[2], Dr. Reena Pant[3], Dr. Krishna Priya Banerjee[3]**

[1]Senior Professor and Head of Department, [2]Resident, [3]Senior Professor, Department of Obstetrics & Gynaecology, SMS Medical College, Jaipur

**Article Info:** Received 03 June 2020; Accepted 4 July 2020
**DOI: https://doi.org/10.32553/ijmbs.v4i7.1277**
**Corresponding author:** Dr Harendra Kumar Netra
**Conflict of interest:** No conflict of interest.

**Abstract**

Background: Maternal and perinatal morbidities are well-documented complications of pregnancy in women with thyroid dysfunction, both clinical and subclinical. About 2–5% of pregnant women suffer from thyroid disorders and timely intervention can be done if detected early. The presence of anti-TPO Ab is associated with increased rate of pregnancy complications such as miscarriage, preterm delivery, placental abruption, pregnancy-induced hypertension, intrauterine death and low birth weight.

Objectives: Study the effect of anti-TPO Ab positivity on pregnancy outcome especially birth weight and estimate the prevalence of anti-TPO Ab in euthyroid pregnant women.

Methods: This observational study enrolled 500 euthyroid pregnant women, age 20-35 years, up to 20 weeks gestation. Venous blood samples collected and analyzed for the anti-TPO Ab levels. On the basis of Ab positivity they were divided into anti-TPO Ab positive and Ab negative group. These two groups were followed up till delivery and compared fetal outcomes for birth weight.

Result: Prevalence of anti-TPO Ab positivity was 5.2% in euthyroid obstetric women. Most of anti-TPO Ab positive women were overweight. Incidence of low birth weight babies was 4 fold higher in anti-TPO Ab positive women.

Conclusion: Anti-TPO Ab positivity significantly associated with prepregnancy BMI and low birth weight of newborns.

**Keywords:** Thyroid peroxidase antibodies, Anti-TPO Ab, Euthyroid, Low birth weight.

## Introduction

Pregnancy may serve as a glimpse into a woman's future health because gestation presents many challenges for various organ systems. Several changes are observed in maternal thyroid function during pregnancy and failure to adapt to these physiological changes results in thyroid dysfunction[1], especially if complicated by the presence of thyroid antibodies.[2]

Subclinical hypothyroidism shows no clinical symptoms but over half of them show evidence of autoimmune thyroid disease by having anti thyroid peroxidase antibodies (anti-TPO Ab) and/or anti thyroglobulin antibodies. Thyroid autoimmunity is the most common autoimmune disorder in women of reproductive age, with a prevalence varying between 4 and 20% depending on the cut-off used and population investigated.[3]

There are no recommendations for the definition of TPO Ab positivity[4]. Instead, cutoffs provided by the assay manufacturers are usually used. So, a wide range of cutoff values (15 to 143 IU/mL) are used to define TPO Ab positivity.

Thyroid peroxidase was first discovered as a thyroidal microsomal autoantigen by Belyavin and Trotter in 1957 and is a key enzyme in the formation of thyroid hormone responsible for catalyzing the coupling of di-iodotyrosine and mono-iodotyrosine.[5] Thyroid peroxidase gene present on chromosome 2p25, is more TSH dependent than thyroglobulin (TG). Anti-TPO antibodies can be of any class of IgG, although some studies indicated a higher prevalence of IgG1 (70%) and IgG4 (66.1%) compared to IgG2 (35.1%) and IgG3 (19.6%).

It has been hypothesized that presence of anti-thyroid antibodies represent a generalized autoimmune imbalance that may be responsible for increased complications despite the euthyroid status. The presence of TPO-Ab is associated with increased rate of pregnancy complications such as miscarriage, preterm delivery, placental abruption, PIH, intrauterine death (IUD), intrauterine growth retardation (IUGR) and low birth weight babies.[6] So, anti-TPO Ab screening test can be an important routine diagnostic tool in early pregnancy which can help to identify women at risk for poor fetal outcome and pregnancy complications.

### Aims and Objectives:

1. To study the effect of anti-thyroid peroxidase antibodies (anti-TPO Ab) positivity on pregnancy outcome in euthyroid women.

2. To estimate and evaluate the prevalence of anti-TPO Ab.

**Material & Methods:**

This hospital based descriptive type of observational prospective study was conducted at department of obstetrics and gynaecology, SMS Medical College, Jaipur during April 2018 to August 2019. 500 euthyroid pregnant women up to 20 weeks gestation between ages 20-35 years were selected as sample size after applying inclusion and exclusion criteria. All participants underwent a comprehensive medical evaluation including a detailed history and a thorough physical examination.

**Inclusion criteria:**

- 20 to 35 years aged euthyroid women with singleton pregnancy up to 20 weeks of gestation.
- Women giving informed and written consent.

**Exclusion criteria:**

- Pregnancy with known autoimmune disorders.
- Cervical incompetence or any uterine malformations.
- Any chronic systemic or medical illness.
- Taking any known thyroid treatments.

**Methodology:**

Serum thyroid stimulating hormone (TSH), T3 and Free T4 was measured in selected pregnant women to ascertain hypothyroid, hyperthyroid or euthyroid status of women. Euthyroid women were selected as study participants. Women diagnosed with abnormal thyroid functions were referred to endocrinology department for treatment. After that 5 ml of venous blood was collected in plain vial from euthyroid women and analyzed for anti-TPO Ab levels by electro-chemilumeniscence immunoassay with "Advia Centaur XP machine" in our central lab (normal value <60 IU/ml). Analytic sensitivity of above assay is 5 IU/ml with a clinical sensitivity and specificity of 98.6% and 98.5% respectively. Trimester and method specific TSH, free T4 and Free T3 values were taken as references as per American Thyroid Association (ATA) 2017.

**Table 1:**

| Reference Range | First trimester | Second trimester | Third trimester |
|---|---|---|---|
| TSH (mIU/L) | 0.1-2.5 | 0.2-3.0 | 0.3-3.0 |
| Free T4 (ng/dL) | 0.8-1.2 | 0.6-1.0 | 0.5-0.8 |
| Free T3 (pmol/L) | 8.04-22 | 9.26-22.12 | 9.54-27.02 |

On the basis of anti-TPO Ab positivity (>60 IU/ml), cases were divided into two groups:-

- Group A- Anti-TPO Ab positive cases and
- Group B- Anti-TPO Ab negative cases.

Following parameters were noted in both groups: age, demographic and socioeconomic status, menstrual history, obstetric history, body mass index (BMI), antenatal investigations and fetomaternal outcomes. Women were followed up till delivery excluding abortions. Data was recorded in a predesigned proforma and maternal and fetal outcomes were noted in both the groups and statistically analyzed by using unpaired t-test for continuous variables while chi-square for normal categorical variables.

**Pregnancy outcome noted as:** Preterm delivery- early preterm (<34 weeks) or late preterm (34 to 37 weeks), PROM, Meconium, Mode of delivery- vaginal or cesarean section, IUD, Apgar score at 1 minute**,** Birth weight, NICU admission and Neonatal death.

**Results:**

**Table 1:** Distribution of Women According to Anti-TPO Antibody

| Anti-TPO Antibody | No. | % |
|---|---|---|
| **Present** | 26 | 5.20 |
| **Absent** | 474 | 94.80 |
| **Total** | **500** | **100.00** |

We screened 500 euthyroid pregnant women for the presence of anti-TPO antibodies, 26 women were found anti-TPO Ab positive and 474 were found Ab negative, hence the prevalence of anti-TPO Ab positivity in euthyroid women were 5.20%.

**Table 2:** Age wise Distribution of Women

| Age Group (in years) | Anti-TPO Antibody | | | |
|---|---|---|---|---|
| | Positive | | Negative | |
| | No. | % | No. | % |
| **20 – 23** | 8 | 30.77 | 142 | 29.96 |
| **24 – 27** | 12 | 46.15 | 190 | 40.08 |
| **28 – 31** | 5 | 19.23 | 96 | 20.25 |
| **32 – 35** | 1 | 3.85 | 46 | 9.71 |
| **Total** | **26** | **100.00** | **474** | **100.00** |
| **Mean Age** p=0.901 | $24.96 \pm 3.13$ | | $24.86 \pm 3.97$ | |

Among anti-TPO Ab positive group, 12 (46.15%) women and among Ab negative group, 190 (40.08%) women were seen in 24-27 years age group with mean maternal age $24.96 \pm 3.13$ years and $24.86 \pm 3.97$ years, respectively. No correlation was observed between mean age & anti-TPO Ab positivity (p=0.901). The association of residence, religion and socio-economic class with anti-TPO Ab positivity is not significant. Most of women were multigravida, 61.54% v/s 60.34% respectively in anti-TPO Ab positive & negative groups.

**Table 3:** Distribution of Women According to Prepregnancy BMI

| BMI ($kg/m^2$) | Anti-TPO Antibody | | | |
|---|---|---|---|---|
| | Positive | | Negative | |
| | No. | % | No. | % |
| **<18.5 (Underweight)** | 1 | 3.85 | 10 | 2.11 |
| **18.5 to 24.9 (Normal)** | 10 | 38.46 | 367 | 77.43 |
| **25 to 29.9 (Overweight)** | 14 | 53.84 | 84 | 17.72 |
| **>30 (Obese)** | 1 | 3.85 | 13 | 2.74 |
| **Total** | **26** | **100.00** | **474** | **100.00** |

The anti-TPO positive group was significantly ($\chi^2$=21.819, d.f=3, p=0.000) overweight as compared to the anti-TPO negative group (p=0.000). Most of anti-TPO Ab positive women were overweight (BMI= 25 to 24.9) while most of anti-TPO Ab negative women were in normal weight group (BMI= 18.5 to 24.9).

**Table 4:** Distribution of Women According to Pregnancy Outcomes

| Pregnancy Outcome | | Anti-TPO Antibody | | | | p-value |
|---|---|---|---|---|---|---|
| | | Positive (n=23) | | Negative (n=462) | | |
| | | No. | % | No | % | |
| IUD | | 1 | 3.85 | 8 | 1.69 | 0.961 |
| Preterm Deliveries | <34 wks | 1 | 3.85 | 10 | 2.11 | 0.921 |
| | 34-37 wks | 2 | 7.69 | 22 | 4.64 | 0.812 |
| PROM | | 1 | 3.85 | 20 | 4.22 | 0.682 |
| Meconium | | 3 | 11.53 | 56 | 11.81 | 0.787 |
| Caesarean | | 5 | 19.23 | 108 | 21.09 | 0.619 |
| Apgar Score | < 7 | 4 | 18.18 | 130 | 28.63 | 0.411 |
| | > 7 | 18 | 81.82 | 324 | 71.37 | |
| NICU Admission | | 4 | 15.38 | 82 | 17.29 | 0.988 |
| Neonatal Death | | 0 | 0.00 | 5 | 1.05 | 0.627 |

There was two times more chance of intrauterine death in anti-TPO Ab positive women compared to anti-TPO Ab negative women (3.85% v/s 1.69%) (p=0.961). PROM, fetal distress (passage of meconium), cesarean section rates, Apgar score, NICU admission and neonatal death had no significant correlation with anti-TPO Ab positivity.

**Table 5:** Birth Weight Distribution of Neonates

| Birth Weight (in kg) | Anti-TPO Antibody | | | |
|---|---|---|---|---|
| | Positive | | Negative | |
| | No. | % | No. | % |
| LBW (SGA + Preterm) | 5 | 22.73 | 29 | 6.39 |
| Normal Birth Weight | 17 | 72.27 | 425 | 93.61 |
| Total | 22 | 100.00 | 454 | 100.00 |

After excluding 3 miscarriages and 1 IUD we reported that out of 22 live births 5 babies (22.73%) born with low birth weight (<2.5 kg) and 17 babies (72.73%) were having normal birth weight (>2.5 kg) in anti-TPO Ab positive group. In anti-TPO Ab negative group out of 454 live births (excluding 12 miscarriages and 8 IUDs) 29 babies (6.39%) had low birth weight and 425 babies (93.61%) had normal birth weight. We observed that irrespective of gestational age, birth weight of newborns was significantly ($\chi^2$=6.162, d.f.=1, p=0.013) affected by presence of anti-TPO Ab positivity (p=0.013). Incidence of low birth weight babies was 4 fold higher in anti-TPO Ab positive women than antibody negative women (22.73% v/s 6.38%).

In our study, rate of preterm delivery at <34 weeks was 3.85% v/s 2.11% respectively, in anti-TPO Ab positive and negative women, while preterm delivery rate between 34-37 weeks in both groups was 7.69% v/s 4.64% that means preterm delivery rate was more in antibody positive group, which was not significant (p>0.05) [Table 4] but there was significant difference between birth weight of newborns in both groups (p=0.013) [Table 5].

**Discussion:**

The maternal physiological changes that occur in normal pregnancy induce complex endocrine and immune responses. In an unselected population of women, the prevalence of thyroid autoimmunity ranges from 4% to 20%. In this study we found the prevalence of anti-TPO Ab positivity in euthyroid women was 5.20% [Table 1]. Similar prevalence was noted by Nambiar V et al (2011)[7]- 5.8%, Meena A et al (2016)[8]- 6% and Meena M et al (2016)- 4%. While higher prevalence reported by Negro R et al (2006)[10]- 11.7%, Karuna et al (2017)[11]- 10.92% and Rajput R et al (2017)[12]- 18.9%. The rates of anti-thyroid antibody positivity are varied in different studies and depend upon the sample size as well as the geographical factors of the study group.

As we know high serum TSH has been associated with adverse pregnancy outcomes, so in our study to remove the confounding effect of TSH levels, we choose euthyroid women as study population.

In our study, most of the women were in the age group of 24-27 years [Table 2] with mean maternal age 24.96 $\pm$ 3.13 years in anti-TPO Abs positive group and 24.86 $\pm$ 3.97 years in Ab negative group. Negro R et al (2006)[10] observed that anti-TPO Ab positive women were older than Ab negative women. Similarly, Meena A et al (2016)[8] noted most of women were in the age group of 25-27 years. While Meena M et al (2016)[9] reported the mean age was 26.95 $\pm$ 3.809 v/s 26.38 $\pm$ 2.826 years. The mean maternal age in both groups was less as compared to Western studies, reflecting early marriage and early conception prevalent in India.

We noted significant association between prepregnancy BMI and anti-TPO Ab positivity (p=0.000) [Table 3]. Most of anti-TPO Ab positive women were overweight. Similarly, Meena M et al (2016)[9] reported that the anti-TPO positive group was significantly overweight as compared to the anti-TPO negative group (p=0.0001). BMI in the anti-TPO positive subjects was 22.472 (SD ±2.81) while in the controls it was 21.93 (SD ±2.02). While Karakosta P et al (2012)[6] and Rajput R et al (2017)[12] observed no significant difference between the BMI and anti-TPO positivity.

We observed two times more chance of intrauterine death in anti-TPO Ab positive women compared to Ab negative women (3.85% v/s 1.69%) (p=0.961). [Table 4] Mannisto T et al (2010)[13] found an increase in perinatal death in anti-TPO Ab positive women. While Rajput R et al (2017)[12] reported no significant association between IUD and anti-TPO Ab positivity in both groups, (2.6% v/s 2%, p= 0.5).

The incidence of preterm delivery (11.54%) was higher in early preterm (3.85%) and also in late preterm (7.69%) in anti-TPO Ab positive women [Table 4] as compared to total 6.75% in anti-TPO Ab negative women (p>0.05). The likely reason for higher incidence of preterm deliveries is that the presence of thyroid autoantibodies reflects a generalized activation of the immune system that would have resulted in deregulation of the immune system against the fetal-maternal interface. Negro R et al (2011)[14] reported the prevalence of very preterm delivery in anti-TPO Ab positive women was 4.5% and 1.8% in Ab negative women (p< 0.01). In a prospective trial, Negro R et al (2006)[10] also reported a significant increase in preterm delivery, 22.4 v/s 8.2% in anti-TPO Ab positive women. On the other hand Karuna et al (2017)[11] found no association between thyroid antibody positivity and preterm labour. However recently, Masoomeh M et al (2019)[15] reported the euthyroid pregnant women with anti-TPO Ab positivity were more likely to go through preterm labor compared with pregnant women without this antibody (21% v/s 4%).

We reported that premature rupture of membrane was found in 3.85% and 4.22% respectively in anti-TPO Ab positive and negative groups (p=0.682) [Table 4]. Similarly, Haddow JE et al (2010)[16] reported an increase in PROM. While, Masoomeh M et al (2019)[15] found less cases of premature rupture of membrane in anti-TPO Ab positive group than anti-TPO negative group (21.1 v/s 70 %).

In our study around equal chances of fetal distress (passage of meconium) in anti-TPO Ab positive and Ab negative women, 11.53% v/s 11.81%, p=0.787. Our study show cesarean rates were low in antibody positive women (19.23% v/s 21.09%, p=0.619). We also noticed non significant relationship about NICU admission (p=0.988) and neonatal death (p=0.627) in anti-TPO Ab positive and negative groups, 15.38% v/s 17.29% and 0% v/s 1.05% respectively [Table 4]. Negro R et al (2011)[14] reported more cesarean section in anti-TPO Ab positive euthyroid women compared to Ab negative euthyroid women (22.4% v/s 20.9%, p=0.560). They also reported more neonatal death in babies delivered from anti-TPO Ab positive euthyroid mothers (0.8% v/s 0.6%, p=0.672) but no difference was observed in NICU admission (5.3% v/s 5.3%, p=0.994).

We observed that irrespective of gestational age, birth weight of newborns was significantly affected by presence of anti-TPO antibodies (p=0.013). Incidence of low birth weight babies was 4 fold higher in anti-TPO Ab positive women than Ab negative women 22.73% v/s 6.38% [Table 5]. Similarly, Meena M et al (2016)[9] found significant association (p< 0.001) between TPO Ab status and birth weight, 25% v/s 5.12% respectively in both groups. Karakosta P et al (2012)[6] noticed increased rates of low birth weight babies in thyroid autoimmune patient. Similar results obtained by Rajput R et al (2017)[12] 10% v/s 5.2%, p=0.09. Meena A et al (2016)[8] reported, rates of preterm delivery at >34 weeks were 5% v/s 1.80% respectively, in thyroid antibody positive and Ab negative women, while preterm delivery rates between 34 and 37 weeks in both groups were 8.33% v/s 3.19%. Although preterm delivery rate was more in antibody positive group, it was not significant (p>0.05), but there was significant difference among birth weights of newborns in both groups (p< 0.001). Gupta Abhilasha et al (2016)[17] found that perinatal outcomes had a significant association with anti-TPO Ab positive status. Those who were positive for anti-TPO Ab 51.02% were premature, 20.43% were IUDs, 54.84% were low birth weight, 48.39% needed NICU admission (p<0.001). While, Negro R et al (2011)[14] reported no significant difference in low birth weight babies between the two groups (6.5% vs. 4.8%, p=0.229). Similarly, Abbassi-Ghanavati M et al (2010)[18] also found no difference in low birth weight babies among anti-TPO antibodies positive and negative women.

Based on reviews from all above studies, in combination with our present study findings, it could be concluded that thyroid antibody positivity is associated with adverse perinatal outcomes.

**Conclusion:**

We concluded from hospital based prospective observational study that prevalence of anti-TPO antibody positivity in euthyroid obstetric population is 5.2% and these autoantibodies are associated with adverse pregnancy outcomes. Incidence of preterm delivery was higher in antibody positive women. Significant association was found between anti-TPO Ab positivity and low birth weight and prepregnancy BMI. Risk of low birth weight babies was 4 fold higher in anti-TPO Ab positive women, therefore universal screening should be considered for thyroid autoimmunity even in euthyroid women.

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