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Original Article

Anti-Thyroid Peroxidase Antibodies in Euthyroid Pregnant Females to Detect Thyroid Autoimmunity

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Abstract

Objective: To show case the early appearance of anti-TPO antibodies, before the onset of thyroid hormone disruption.

Methods: It was a cross-sectional study in which 227 antenatal women who were euthyroid (normal free T4 and free T3 levels) were included and their Anti-TPO antibodies were analysed and recorded.

Results: The mean age of the pregnant females was 25.67 ± 4.531 years and the mean gestational age was 25.18 ± 9.214 weeks. Among 227 pregnant females, 97.8% had anti TPO antibodies levels in the 0-30IU/ml range while only 2.2% had >30IU/ml. The mean anti TPO level among pregnant females was 7.020 ± 4.004IU/ml. There was significant association ($p<0.05$) between trimesters and anti TPO Ab level while insignificant association ($p>0.05$) of anti TPO Ab with gravidity, parity and abortion.

Conclusion: Study concluded that adding anti-TPO antibodies together with markers of thyroid function such as TSH, FT4 and FT3 is not cost effective in identifying pregnant females who might develop thyroid dysfunction and associated pregnancy loss, preterm birth. The prevalence of Anti TPO Ab in euthyroid pregnant females in our study was only 2.2%.

Keywords: Anti thyroid peroxidase antibodies, thyroid-stimulating hormone, free thyroxin, euthyroidism, pregnancy

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Introduction

Thyroid hormones are of paramount significance when it comes to brain and somatic development among infants and of metabolic activity among adults. They have critical effect on the function of all organ systems.

The TAI (thyroid autoimmunity) seems to be an important determining factor in pregnancy loss. Several researches have reported this relationship, not just among hypo or hypethyroid females but also among euthyroid females.[1] There are three hypotheses that explain this relationship:

1. Thyroid antibodies can represent an indicator of a generalized autoimmune imbalance responsible for an enhanced frequency of miscarriage.
2. In spite of lab euthyroidism, females found to have thyroid antibodies positive prior to pregnancy can develop overt/subclinical hypothyroidism during the period of pregnancy. There is always a risk that a preexisting slight thyroid dysfunction can get worse during the period of pregnancy (particularly during 1st trimester). Thyroid antibodies effects among patients with thyroid disorders have been well recognized however their effect among euthyroid females is an arguable issue so far.
3. Because TAI shows a risk factor regarding infertility, females with antibodies are mostly older than those with no antibodies and that could explain

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the enhanced frequency of pregnancy loss.[2-4]

Euthyroidism is defined as normal thyroid function proven by normal serum levels of thyroid-stimulating hormone(TSH) and free thyroxin(FT4). Subclinical hypothyroidism is described biochemically as a normal serum free thyroxin (T4) concentration in the presence of a raised serum TSH concentration. There is a negative log-linear association between serum TSH and FT4 concentrations[1]. It means that very small alterations in the serum FT4 concentrations induce very large reciprocal alterations in the serum TSH concentrations. Consequently, thyroid function is best evaluated by measuring the serum TSH, assuming steady-state conditions.

In opulation-based researches, subclinical hypothyroidism prevalence ranges from 4-15%.[5,6] The incidence increases with increasing age and found elevated among women more than men as well as among whites more than blacks.[5-8] A study showed that frequency of the subclinical hypothyroidism was 4.2 percent in iodine-deficient region and 23.9 percent in a region with abundant iodine consumption, but high serum concentrations of anti-TPO antibodies.[9]

The Anti thyroid peroxidase antibody is the most prevalent anti-thyroid autoantibody, found in about 90 percent of Hashimoto's thyroiditis and 75 percent of the Graves' disease while 10-20 percent of the nodular goiter / thyroid cancer. Interestingly, 10-15 percent euthyroid persons can have elevated anti-TPO antibody titer levels.

Iodine is essential for normal thyroid function, and it can be acquired only by foods consumption that have it or to which iodine is included. During the period of pregnancy & lactation, iodine amount 250 mcg daily is recommended by WHO.

Thyroid hormone synthesis begins with iodine absorption. Nutritional iodine is absorbed as iodide and distributed quickly in extracellular fluid that also holds iodide discharged from thyroid gland and by the extra-thyroidal de-iodination of iodothyronines. The iodide leaves this pool via transport in thyroid and excretion in urine.[10]

Role of thyroid peroxidase(TPO) is very important. In thyroid follicular cells, iodide is transferred through pendrin to exocytotic vesicles combined with apical cell membrane.[1] The iodide in these vesicles is oxidized and organified to a few of the tyrosyl residues of thyroglobulin. This oxidation of iodide is catalyzed through TPO. Thyroxin(T4) is created by the coupling of 2 diiodotyrosine remains while T3 by the coupling of one diiodotyrosine and one monoiodotyrosine in a thyroglobulin molecule. These reactions are also catalyzed by TPO.

Approximately 75% of T4 is bound to TBG (thyroid binding globulin), 10% to TTR (transthyretin), 3% to lipoproteins and 12% to albumin. About 0.02% or 2ng/dL (25pmol/L), of T4 in serum is free.

For T3, about 80.0% is bound to the TBG and 15.0% to lipoproteins & albumin while 5.0% to TTR. Just about 0.5% or 0.4ng/dL (6pmol/L), of the T3 in serum is free. Production of TBG is increased 2-3 fold during pregnancy and T3 and T4 to about 30-100%[11] but free T4 and free T3 remain the same that is why it is essential to request free levels of T4 and T3 for accurate estimation of thyroid function[2-4]. The free hormone hypothesis states that the unbound or free hormone is the fraction that is available for uptake in the cells and for interaction with the nuclear receptors.

Approximately 1 in 10 pregnant women develop Thyroid autoimmunity in first trimester and roughly 16% develop subclinical hypothyroidism later in pregnancy.[12]

So, hypothyroidism may be predicted at the onset of pregnancy on the basis of TPOAb titers and TSH value, so that patients having TSH above 2.0 mIU/liter and/or high TPOAb (above 2000 kIU/liter) are more likely to develop overt thyroid dysfunction,[14] during pregnancy and more so during postpartum period, can be identified and put under vigilant surveillance.

The objective of the study was to evaluate the presence of anti-TPO antibodies in euthyroid pregnant females and predict onset of thyroid hormone disruption; hoping the addition of anti-TPO antibodies on top of traditional thyroid function markers TSH, FT4 and FT3 would aid to reduce untoward pregnancy outcomes and manage long-term morbidity.

Methods

It was a cross-sectional study conducted among antenatal women attending OPD of Ghurki Trust Teaching Hospital Lahore and Jinnah Hospital Lahore after approval of synopsis from the ethical review board of Lahore Medical & Dental College. The duration of study was 6 months. During study 450 pregnant women were selected with no history of known thyroid disease in self or in family. Five ml of blood sample was drawn, under aseptic conditions, from each subject for measurement of their serum free T3, free T4, TSH. The samples

were labeled and centrifuged within half hour. The serum of each patient was put into sterilized Eppendorf 5ml screw cap tubes. It was then transported to Chemical Pathology lab of Central Park Medical College Lahore in sample transport containers daily. The samples, which were not analyzed immediately were then stored at -20°C. Among these pregnant women, 227 were found to be euthyroid on the basis of operational definition and included in the study and their Anti-TPO antibodies were checked. Maglumi 800 chemiluminescence immunoassay (CLIA) system was used to measure serum FT3, FT4, TSH, Anti TPO antibodies in the collected samples. The tests were carried out in batches of 20 after collection. The normal range of Free T3(2-4.2pg/ml), Free T4(8.9-17.2pg/ml), TSH(0.3-4.5 uIU/ml) and Anti TPO Ab(0-30IU/ml) was considered according to the reagent used. Women taking drugs that could change thyroid levels, those with autoimmune disorders, chronic hyperten-sion, diabetes mellitus, known thyroid disorder, with congenitally malformed fetus and not willing to take part in the study were excluded. A questionnaire was prepared containing age, trimester, obstetric history, TSH, FT3, FT4 and Anti TPO anti-bodies. The data was analyzed using SPSS version 24.0. Frequencies and percentages were calculated for qualitative data, while mean+SD was calculated for quantitative data. Chi-square test was applied to find out association. A P-value <0.05 was considered statistically significant. Confidentiality of the data was ensured and proper consent was obtained prior to data collection.

Results

Two hundred and twenty-seven women were euthyroid as their TSH was in range 0.3-4.5IU/ml and Free T4 was between 8.9-17.2pg/ml.

Among 227 pregnant females, 192 (84.6%) wre 18-30 years old while only 35 (15.4%) were 26-45 years old. The mean age of the pregnant females was 25.67 + 4.531 years.

Forty-one (18.1%) pregnant females were in their first trimester and 82 (36.1%) were in their second trimester while the majority 104 (45.8%) were in their third trimester. The mean gestational age was 25.18 + 9.214 weeks as depicted by figure-1.

Out of 227 pregnant females, 87 (38.3%) were primi-gravidas and 140 (61.7%) were multigravidas. The mean gravidity was 2.20 + 1.373.

Sixty-nine out of 227 pregnant females (30.4%), were primiparas and 59 (26.1%) were multiparas while only 3 (1.3%) were grand multiparas. The mean parity was 1.02 ± 1.165. Majority 189 (83.3%) had no abortion while 35 (15.4%) had 1-2 abortions and only 3 (1.3%) had >2 abortions. The mean abortion was 7.020 ± 4.004.

Among 227 pregnant females, 222 (97.8%) had anti TPO antibodies levels between 0-30IU/ml which is normal or negative, while only 5 (2.2%) had >30IU/ ml which makes them positive for TAI. This holds key significance in our study as shown in Figure-2. The mean anti TPO level among pregnant females was 7.020 ± 4.004. In the Anti TPO Ab positive group One (20%) was primigravida while four (80%) were multi-gravidas. There was no significant association between parity of females. Four females were Anti TPO Ab positive with no previous history of abortions. And one was positive with history of one abortion.

Figure-2 shows the association($p<0.05$) between tri-mesters and anti-thyroid peroxidase antibodies.

Table-1 demonstrates the association between thyroid function tests and different trimesters. Result shows that there was insignificant association ($p>0.05$) between thyroid function tests and different trimesters. But a significant association was found between Anti TPO Ab and different trimesters. Mean FT4 was 11.21±1.69 pg/ml, mean FT3 2.75±0.83pg/ml and mean TSH 1.53 ± 1.89uIU/ml.

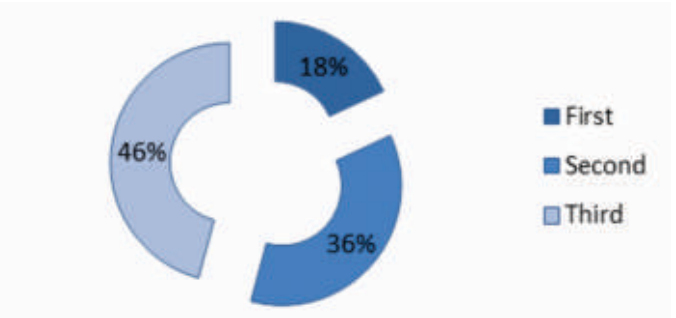

Figure-1: *Frequency Distribution of Pregnant Females According to Trimester*

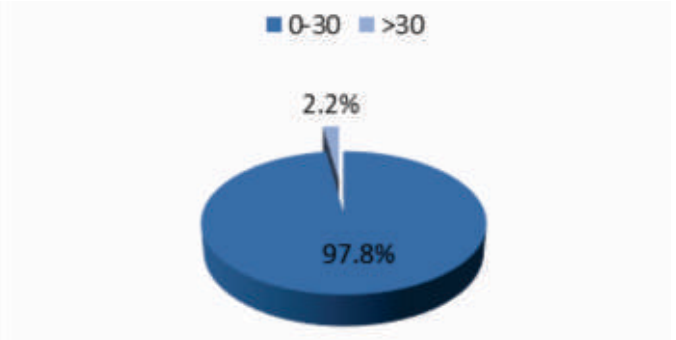

Figure-2: *Frequency Distribution of Euthyroid Pregnant Females According to Anti Thyroid Peroxidase Antibody(IU/ml)*

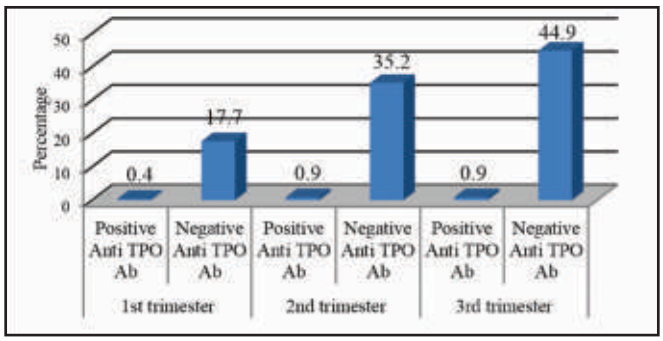

Figure-2: *Association between Trimesters and Anti-Thyroid Peroxidase Antibodies(IU/ml)*

Discussion

Anti-thyroid peroxidase antibodies are leading problem among pregnant females which increases the incidence of pregnancy loss, preterm birth. Present study "Anti Thyroid Peroxidase Antibodies in Euthyroid Pregnant Females" was carried out at Ghurki Trust Teaching Hospital Lahore and Jinnah Hospital Lahore. To acquire appropriate outcomes, 450 pregnant women were selected with no history of known thyroid disease in self or in family. TSH, Free T4 and Free T3 were performed. Among these pregnant women, 227 were found to be euthyroid on the basis of operational definition and included in the study. Anti-thyroid peroxidase antibodies were checked among these women.

Study revealed that 84.6% of the females were in 18-30 years age group while remaining 15.4% were in 26-45 years age group and mean age of the pregnant females was 25.67 ± 4.531 years. The findings of our study are almost comparable with a study undertaken by Elhaj and teammates (2016) who reported that mean age of the pregnant females was 27.0 ± 4.9 years.[13]

It was found during study that 45.8% of the pregnant females were in their third trimester, followed by second trimester (36.1%) and first trimester (18.13%). A study carried out in 2019 by Almomin and Mansour highlighted that most of the pregnant females (45.1%) were in their second trimester, followed by third trimester (30.3%) and first trimester (24.6%).[14]

Table 1: *Thyroid Function Tests and Antithyroid Peroxi-Dase Antibodies in different Trimesters, Mean and SD Ratio*

	Trimesters			Mean	P-value
	1st	2nd	3rd		
FT3 (pg/ml)	2.974± 0.975	2.912± 0.737	2.535± 0.930	2.751± 0.893	0.106
FT4 (pg/ml)	12.137 + 2.073	11.188+ 1.563	10.870+ 1.511	11.212± 1.699	0.177
TSH uIU/ml	0.928± 0.701	1.590± 1.248	1.723± 2.511	1.531± 1.898	0.090
Anti TPO Ab IU/ml	1.769± 9.297	3.979± 7.220	5.210± 8.004	7.020± 4.004	0.025

Thyroid disorders are common among pregnant females that increase the risk of abortion and other complications. Study disclosed that among pregnant females, mean gravidity was 2.20 ± 1.373 and mean parity was 1.02 ± 1.165 while mean abortion was 0.22 ± 0.558. The findings of a similar study conducted by Elhaj and teammates (2016) indicated that mean gravidity among pregnant females was 2.5 ± 4.0 while the mean parity was 0.8 ± 1.1.13

Study showed very encouraging results that among 227 pregnant females, major proportion (97.8%) had normal anti TPO Ab level (0-30IU/ml) and only 2.2% pregnant females were found positive for anti TPO antibodies(>30Iu/ml). The findings of our study are much better than a most recent study undertaken by Ning Yuan and Colleagues (2020) at Peking University International Hospital, who confirmed that 10.7% euthyroid pregnant females were found positive for anti TPO antibodies.[15] According to Almomin & Mansour (2019)1410.1% of their euthyroid pregnant females were Anti TPO Ab positive. Karuna et al (2017)[16] showed the study results in a different manor. Their Anti TPO positivity was 21.3% (49 0f 229) but out of these patients only 25 were euthyroid and 24 hypothyroid. So Anti TPO Ab positivity comes out to be 10.9%. Our Anti TPO Ab positivity rate in euthyroid pregnant females is far less than the above mentioned studies. On the other hand, a study conducted by Plowden et al shows a total positivity of 5.5% of Anti TPO Ab in their sample pregnant females.[17]

When the association between obstetric history and anti TPO antibody was assessed, no significant association (P>0.05) of anti TPO was found with gravida, parity and abortion. Kiran and fellows (2021)[18] also reported in their study that there was insignificant association (P>0.05) of anti TPO Ab with parity and abortion.[18] In another study, Karuna et al. (2017) found a two-fold rise in the pregnancy loss among TPO antibodies positive females when compared with TPO antibodies negative females. Though, the abortion rate in euthyroid females irrespective of thyroid peroxidase antibodies status was same (2.52% versus 3.06%).[16]

As far as association between trimesters and thyroid

function tests is concerned, study showed that there was insignificant association (P>0.05) between thyroid function tests and different trimesters. But a significant association was found between Anti TPO Ab and different trimesters. The increase in TSH mean levels was observed from first trimester to third trimesters while FT3 and FT4 mean levels were decreased from first trimester to third trimester. The mean levels of Anti TPO Ab were also increased from first trimester third trimester. A similar study carried out by Elhaj and teammates (2016) showed an increasing trend from first trimester to third trimester for TSH but decreasing trend for FT3 and FT4 from first trimester to third trimester.[13] A study carried out by Elebrashy and coworkers (2019) indicated that Anti TPO Ab mean levels were decreased from first trimester to third trimester with significant results (P<0.001).[19]

Conclusion

Anti-thyroid peroxidase positivity is common problem among pregnant females. Study concluded that addition of anti-TPO antibodies together with traditional thyroid markers such as TSH, FT4 and FT3 is not cost effective in preventing pregnant females from thyroid dysfunction and associated pregnancy loss and preterm birth. American Thyroid Association Guidelines in pregnancy also indicate that there is insufficient data to recommend for or reject screening or treating all pregnant women for thyroid auto-antibodies

Conflict of Interest: None

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Authors Contribution

S.A: Conceptualization of Project, Data Collection, Writing of Manuscript, Literature Search

M.A: Data Collection, Statistical Analysis

S.N: Drafting, Revision

N.U: Literature Search