Association of Anti-thyroid Peroxidase Antibody Among Euthyroid Women with Adverse Pregnancy Outcomes

Original Article

Mai M. Shaker, Taghreed A. Shalabi

Prenatal Diagnosis and Fetal Medicine Department, Human Genetics and Genome Research Institute, National Research Centre, Cairo, Egypt.

ABSTRACT

Background: Thyroid autoimmunity (TAI) can have an adverse impact on pregnancy outcomes. Thyroid peroxidase (TPO) is a main enzyme needed in thyroid hormones; important autoantigen in autoimmune thyroid diseases.

Patients and Methods: It is a prospective study. 250 women in euthyroid state were screened for positive existence of anti-TPO Ab. 40 out of 250 were positive for anti TPO antibodies. Those 40 Euthyroid pregnant females were observed, and outcomes were compared to gestation matched controls pregnant women (anti-TPO negative) using Elisa.

Results: Anti-TPO positivity among screened pregnant women was 16%. Anti-TPO positive, euthyroid females had a higher occurrence of pregnancy loss 22.5% vs. 5%; p <0.05, preterm labor 25% vs. 7.5%; p <0.05. Pregnant women positive for anti-TPO Ab had higher risk for pregnancy loss (5 folds) and for preterm labor (4 folds) in comparison to the control. There was no statistical significance detected between cases and controls regarding hypertension, anemia, diabetes, IUGR and IUFD; p >0.05 respectivly.

Conclusion: There is correlation between the presences of anti-TPO antibodies among pregnant women with adverse pregnancy outcomes in euthyroid state pregnant women.

Key Words: Antibodies, Outcome, Peroxidase, Pregnancy, Thyroid.

Received: 11 December 2023, **Accepted:** 27 February 2024

Corresponding Author: Mai Shaker Phd, Prenatal Diagnosis and Fetal Medicine Department, Human Genetics and Genome Research Institute, National Research Centre, Cairo, Egypt. **Tel.:** +244867234, **E-mail**: maishaker777@gmail.com

ISSN: 2090-8571, 2023

INTRODUCTION

One of the essential catalysts involved in the synthesis of thyroid hormones is thyroid peroxidase (TPO). It is a foremost important auto antigen in autoimmune thyroid disorders. Autoantibodies to TPO (TPOAb) is measured as secondary response and highliting the presence of thyroid inflammation. It is found in 10–20% of females at reproductive age. TPOAbs are produced by activating immunological response in the thyroid gland, however the vast majority of females with elevated thyroid autoantibodies are in euthyroid state with a normal thyroid hormone level including ; free triiodothyronine (FT3), free thyroxine (FT4) and Thyroid stimulating hormone (TSH) (**Balucan *et al.*, 2013; Chen *et al.*, 2022**).

During gestation period any turbulence in thyroid function might raise the risk for associated pregnancy co-morbidities. For example; preterm labor, placental abruption, intrauterine fetal death, preeclampsia (**Cleary-Goldman *et al.*, 2008; Seungdamrong *et al.*, 2017; Andersen *et al.*, 2018; Tańska *et al.*, 2023**). Several researches reported that disorders in thyroid gland functions are one of the commonest endocrine conditions that can affect females during childbearing period. Auto immune thyroiditis can interrupt the normal course of pregnancy as well as the pregnancy outcome (**Bagis *et al.*, 2001; Alijotas-Reig and Garrido-Gimenez, 2013; Kyrilli *et al.*, 2023**). Around 17-19% of women during their child bearing period acquire positive titers for anti-TPO Ab (**McElduff and Morris, 2008; Dhillon-Smith and Coomarasamy, 2020**). Despite the fact, that the influence of auto immune thyroiditis among females with thyroid disorders had been widely studied, yet the impact of (anti-TPO Ab) among euthyroid females still remains a controversial topic. There is a similarity between women in euthyroid state and women with Subclinical hyperthyroidism in which both have normal serum thyroid hormone levels and circulating thyrotropin values (**Dong *et al.*, 2020**). The concept of "normal" TSH levels affects the biochemical basis of the diagnosis. The National Health and Nutrition Examination Surve established the reference range for serumTHS levels between 0.45 and 4.5 U/mL in 2002 (**Hollowell *et al.*, 2002**). *Stagnaro* and his colleagues conducted a study,

© 2023 Middle East Journal of Medical Genetics | National Society of Human Genetics - Egypt *DOI: 10.21608/MXE.2024.254631.1010*

which was a milestone. They highlighted a correlation between adverse pregnancy outcome and the existence of anti-thyroid antibodies among euthyroid pregnant females (**Stagnaro-Green *et al.,* 1990**). Till these days, it's not clear the exact pathophysiology leading to poor pregnancy outcome among anti-TPO positive females. However, its theorized that the existence of anti-TPO antibodies denote a widespread of autoimmune imbalance which might be the triggering point for the cascade of complications during gestation period. It is reported that pregnant females might have high level of thyroid antibodies while being in the euthyroid state and this increase the liability to fall into mild form of hypothyroidism during gestation period.

TSH hormone tiggers production of thyroid hormones. The main enzyme responsible for TSH activation is Thyroid peroxidase (TPO). Anti–TPO antibodies (Anti–TPO Ab) antagonize the function of the TPO enzymes and consequently leads to thyroiditis (**Xu *et al.,* 2023; Trbojević and Djurica, 2005**). However there is no solid proof that anti-TPO Ab have a big role in thyroid impairment (**Vargatu, 2016**). Though, there are several studies irrespective to thyroid autoimmunity inspesfic discussed the autoimmune disturbances among pregnant women and its impact on pregnancy outcome (**Ünal *et al.,* 2019; Tanacan *et al.,* 2019; Mumusoglu *et al.,* 2016**). But in our study, we excluded those patients to focus mainly on correlation of anti-TPO positivity with pregnancy outcomes.

It had been stated that anti-TPO positive pregnant females might previously had a subclinical thyroid impairment but due to the growing needs during gestation period the general condition might deteriorate and clinical symptoms starts to appear. anti-thyroid anti-TPO Ab theoretically might cause infertility and increased chances for pregnancy loss (**Negro *et al.,* 2006**). Up to our knowledge there is no considerable Egyptian data involving our population discussing thoroughly and available regarding this topic. We aimed by this study to evaluate the frequency of anti-TPO Ab among pregnant women and asses the correlation of anti-TPO positivity with pregnancy outcome among euthyroid women in comparison to healthy pregnant females who were negative for anti-TPO Ab.

PATIENTS AND METHODS:

1. Study Design:

It is a prospective study. Two hundred and fifty pregnant females who came for antenatal care and follow up at our outpatient clinic of our department were screened for the existence of anti -TPO Ab in their first 20 weeks of the gestation period to evaluate its occurence. Participants were offered prenatal counseling as well as detailed pedigree analysis and history taking.

Selection of cases

Inclusion criteria: Pregnant women in a reproductive age (20-35) years having a normal TSH level ranging from 0.4 to 7 uIU/mL (euthyroid state). Euthyroid pregnant females with raised anti-TPO antibodies >75mg/dl were carefully chosen from this population forming the case group (Table 2). Pregnant females among case group must have at least one child live birth.

Exclusion criteria: subjects having any abnormality in one of the following investigations; thyroid profile (T3,T4,TSH), karyotypes, hormonal assays for ex: progesterone and thyroid function, uterine anomalies were excluded. Exclusion criteria also included women with regular intake of drugs which might affect the thyroid levels, autoimmune abnormalities for ex:(anti nuclear anti bodies, antithyroglobulin, Anticardiolipn antibodies, systemic lupus). Diabites, hypertension, those already diagnosed with thyroid disorders and current pregnancies were fetuses having multiple congenital anomalies; anemia (hemoglobin level <10g/dL); obesity (BMI >30) and bad obstetrics history (2or more consecutive abortions) were also excluded from the study. Pregnancy outcomes among anti-TPO positive euthyroid females was recorded in comparison to control group. To guarantee a safeguard comparison between both studied groups, The controls' gestational age was the same as the matched study women's at the time a blood sample from them was taken.

Forty pregnant women without this antibody (anti-TPO negative), gestational aged matched who were selected as control group by simple random sampling of the pregnant population. Written informed written consent was obtained from all participants before sampling. Ethical approval numbered (19266) was obtained from the Medical Research Ethical committee of our institute. This research article was drived from a research funded Project which was reviwed by IRB committee, from the National Research Center; Cairo, Egypt. Project Fund number (12060180). All pregnancy outcomes were recorded for both groups including; hemoglobulin level for anemia (tested in the first trimester), preterm delivery, pregnancy loss, intra uterine growth retardation (IUGR), intra uterine fetal death (IUFD), gestational diabetes, and gestational hypertension.

Specimen collection

All women had blood from their peripheral veins drawn in a total of 3 millilitres, during second trimstere (weeks 13–22). To minimise the pre-analytical discrepancy, obtained serum was obtained and managed in accordance with operating method. Peripheral blood samples were centrifuged at 4°C for 5 minutes at a speed of 4000 rpm to separate the serum, and then at 4°C again for 5 minutes at a speed of 14000 rpm to remove any residual cells. Aliquots of serum were kept at -20 degrees Celsius for storage.

Serum anti-TPO Ab, free triiodothyronine (FT3), free thyroxine (FT4), and TSH was measured during the first trimester. Thyroid parameters serum levels were analysed using ELISA (DRG International Inc., Germany) method in both the cases and controls following manufacture protocol.

2. Statistics:

The IBM Corp., Armonk, NY, USA used IBM SPSS Statistics version 22 to conduct the statistical study. The mean standard deviations, relative frequencies, frequency distribution, and percentages of the variables were calculated. Using the Student t-test for independent samples, parameters with normal distribution were compared.

RESULTS

Out of 250 pregnant female screened for the existence of anti-TPO Ab, 42 were anti-TPO positive, therefore, the occurrence of anti-TPO positivity was 16%. Among this group who were anti-TPO positive, 2 women were in hypothyroid state having a TSH value above the normal range (0.4-7.0 mIU/ml) so they were excluded. Only 40 women were found to be anti-TPO positive with TSH being in the euthyroid range. Those women formed the study group, and followed up until delivery. Equivalent number of pregnant females who were anti-TPO antibodies negative, matched in gestation and parity formed the control group.

The mean age of case group (27±4) years of age [mean±standard deviation (SD)] vs. (25±3) years among controls with statistical significant P <0.001. There were no significant differences between both groups regarding body mass index (BMI) and parity; P >0.05, as shown in (Table 1).

Anti TPO levels elevated among case group with an average of 90±7.4 in comparison the control group who were with in normal range for anti TPO levels 19±5.3. Having confidence interval and P value of (CI: 68.13-73.87, P <0.0001). While mean of TSH levels were with in normal range for both studied group; (3.6±0.7) and (3.2±1.0) for case group and control group with confidence interval and P value of (CI: 0.016-0.784, P= 0.07) as shown in table 2.

22.5% pregnant females (n= 9/40) in the case group (anti-TPO Ab positive), went through pregnancy loss in comparison 5% (n= 2/40) in the control group (anti-TPO Ab negative). 25% (n= 10/40) had gone through preterm labor in the case group in comparison to only 3 pregnant females (7.5%) had gone through preterm labor in the control group with a statistically significant difference P <0.05, Table 3. In reference to the calculated odds ratio (OR), pregnant females positive for TPO Ab had a higher risk for pregnancy loss (5 folds) and preterm delivery (4 folds) respectively, in comparison to the number of females in the control group; OR;(95% confidence interval (CI))= 5.5(1.1-27.4) and 4(1.0-16.2), Table 3. Most of the pregnancy loss had occurred at mean of gestational age 9 weeks for both studied groups. women went through preterm labor around the mean of 31.2 weeks for the case group and 32.6 weeks for the control group, having a statistically significant difference P= 0.04. There was no statistical significance detected between cases and controls regarding the occurrence of the subsequent outcomes; hypertension, anemia, diabetes, IUGR and IUFD; as shown in (Table 3; Figure 1).

Table 1: Clinical parameters of TPO Positive and TPO Negative groups:

Parameters	Anti-TPO Positive (n= 40) (Mean±SD)	Anti-TPO Negative (n= 40) (Mean±SD)	*P* Value
Age (years)	27±4	25±3	0.001*
BMI (kg.m^2)	24±3	25±3	0.379
Parity	1.8	2.1	0.164

† TPO: Thyroid peroxidase antibody; BMI: Body mass index; ±SD: Slandered deviation; *P <0.05 is considered significant.

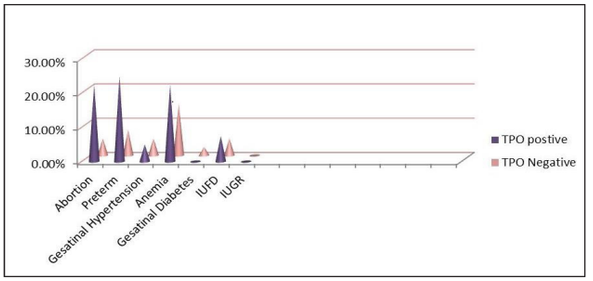

Figure 1: Display the frequency of different pregnancy outcomes between TPO positive pregnant women and TPO negative pregnant women; *IUFD*: intrauterine fetal death; *IUGR*: intrauterine growth retardation.

Table 2: Thyroid parameters of TPO Positive and TPO Negative groups:

	Anti-TPO Ab Positive (Mean±SD)	Anti-TPO Ab Negative (Mean±SD)	(95% CI)	Std error	*P* value
TSH $_{Range}$ (0.4-7) uIU/mL	3.6±0.7	3.2±1.0	0.016-0.784	0.2	0.07
TPO Ab $_{Positive}$ (>75) IU/mL	90±7.4	19±5.3	68.13-73.87	1.4	<0.0001*

†TPO: Thyroid peroxidase antibody; TSH: Thyroid Stimulating hormone; CI: confidence interval; std error: slandered error; *P <0.05 is considered significant.

Table 3: Frequency of different outcomes among TPO positive and TPO negative pregnant women:

Outcome		Happened/Didn't Happen	Anti-TPO Ab Positive *n*= 40 (%)	Anti-TPO Ab Negative *n*= 40 (%)	*P* value, OR (95%CI)
Normal		Happened	7(17.5%)	24(60%)	<0.001; 7(2.5-19.8)
		Didn't Happen	33	16	
Poor	Pregnancy loss	Happened	9(22.5%)	2(5%)	0.03; 5.5(1.1-27.4)
		Didn't Happen	31	38	
	Preterm	Happened	10(25%)	3(7.5%)	0.04; 4(1.0-16.2)
		Didn't Happen	30	37	
	GHT	Happened	2 (5%)	2(5%)	-
		Didn't Happen	38	38	
	Anemia	Happened	9(22.5%)	6(15%)	0.4; 1.6(0.5-5.1)
		Didn't Happen	31	34	
	GD	Happen	-	1(2.5%)	-
		Didn't Happen	40	39	
	IUFD	Happened	3(7.5%)	2(5%)	0.64; 1.5(0.2-9.7)
		Didn't Happen	37	38	
	IUGR	Happened	-	-	-
		Didn't Happen	40	40	

†TPO: Thyroid peroxidase antibody; IUFD: intrauterine fetal death; IUGR: intrauterine growth retardation; GHT: Gestational Hypertension; GD: Gestational diabetes; OR: odds ratio; CI: confidence interval; **P* <0.05 is considered significant.

DISCUSSION

Anti-TPO Ab are secreted mostly by lymphocytes attacking mainly the thyroid gland and to a lesser extent its also secreted from bone marrow and regional lymph nodes (**Trbojević and Djurica, 2005**). Anti-TPO Ab prompots the damage of thyroid cells mainly by the excessive stimulation of the complement besides enhancing cell cytotoxicity (**Chardès *et al.,* 2002**). In our study, there was no statistically significant difference between anti-TPO Ab positive females and anti-TPO Ab negative females regarding BMI and parity. Though both groups were in reproductive age (20-35) years, the case group was statsically significantly older than control group (27±4) vs. (25±3) years. group *P* <0.001. This finding can be atttrbuted to the presence of age-linked resistance to thyroid hormones which might happen due to the following reasons; poor cell membrane carriage of thyroid hormone, disfunction of cell nucleas receptors for thyroid hormone as well as mal function of cytosol deiodinase enzyme as individuals grow older in age (**Mooradian, 2023**). A study proved correlation of anti-TPO Ab levels and aging, where there is different levels of antithyroid antibodies among individulas in different age groups (**Surks and Hollowell, 2007**). Several studies also stated that anti-TPO Ab was more predominate among woman who were older in age in comparison to controls (**Negro *et al.,* 2006; Stricker *et al.,* 2007**). In contrast to our findings regarding parity a study done by (**Glinoer, 2011**), stated that anti-TPO Ab was more predominate among females who were multiparous in comparison to females who were primigravida.

In our study there was a strong correlation between presence of anti-TPO positivity in pregnant females and the incidence of sponteanous abortion (SA) and preterm labor; (22.5% vs.5%) and (25% vs.7.5%) respectively. Similar conclusion to our findings was reached by several studies For example, (**Rajput *et al.,* 2017**) stated that great percentage of females during their gestation period were positive for Anti-TPO Ab and their was great association with SA as well as preterm birth incidences. 16% to 34% of females who had a history of recurrent spontaneous pregnancy loss encountered agreater anti-TPO antibody level in comparison to controls (**Thangaratinam *et al.,* 2011; Karakosta *et al.,* 2012; Ghalib *et al.,* 2023**). The association between TPO antibodies among euthyroid pregnant females and risk of SA and other poor pregnancy outcomes was also supported by multiple recent met analysis (**Dhillon-Smith and Coomarasamy, 2020; Zhang *et al.,* 2023**). Furthermore, it was also documented that 11% to 32% of females who had a history of infertility, are more likely that they have anti-TPO Ab level that is greater than any other pregnant females (**Andersen *et al.,* 2018**). In a study anti-TPO Ab prevalence was 5.2% among euthyroid pregnant females. with agreat percentage of abortions (11.54%) vs. (2.53%) in anti-TPO Ab negative females. Even Frequency of small birth weight off springs was four fold more prevalent among anti-TPO Ab pregnant females (**Netra *et al.,* 2020**). Similarly, *Masoomeh* and his colleagues reported that prevalence of miscarriage was significantly greater 19% among anti-

TPO Ab positive pregnant females in comparison to anti-TPO Ab negative pregnant females 5.7%. With a *P* value <0.001 (**Masoomeh *et al.,* 2019**) Existence of anti-TPO Ab in spite of normal thyroid function, may increase the risk for spontaneous pregnancy loss and preterm labor up to 5 folds (**Vissenberg *et al.,* 2016; Poppe *et al.,* 2008; Liu *et al.,* 2022**). In disagreement to our finding, a study reported that there was no statistical difference regarding SA with presence of antiTPO-Ab by comparing positive antiTPO-Ab levels with negative anti TPO-Ab levels among euthyriod pregnant females; *P*= 0.116 (**Beksac *et al.,* 2022**). A prospective study demonstrated that females positive for anti-TPO Ab had a 3 fold higher risk for neonatal death in comparison to females negative for anti-TPO Ab. One of the reasons for this high neonatal mortality rate is due to the rise in the frequency of preterm labor produced secondarily to the rise of anti-TPO Ab in maternal circulation (**Abalovich *et al.,* 2013**). *Li* and his colleagues conducted a non-randomized controlled clinical trial. They reported that the number of positive anti-TPO Ab females and were in euthyroid thyroid state, after they took levothyroxine during gestation period and admitted to intensive care were much less in comparison to the number of females who did not take clinical trial treatment (**Li *et al.,* 2022**). Conferring to the American Thyroid Association's 2011 Guidelines, there is no sufficient proof to encourage or reject conducting a wide screening tests for the existence of anti-TPO Ab among pregnant females or even to treat anti-TPO Ab positive euthyroid females with levothyroxine (**Jonklaas *et al.,* 2014**). While *Van Dijik* and his colleagues were against this theory. He gave palliative extra levothyroxine as a treatment, and no increase in the living birth percentage was observed, consequently did not praise levothyroxine among euthyroid females having SA as atreatment (**Van Dijk *et al.,* 2022**).

The probable explanations for the high rate of SA with anti-TPO positivty ocuuring among pregnant females is that those anti-TPO positive females have subclinical insufficiency for thyroid hormone and then face difficulty to fulfill the required increased needs during gestation period (**Gameil *et al.,* 2023**). Also, it had been assumed that the existence of anti-TPO Ab is a sign of generalized autoimmune disease which harmfully affects the embryo intra urine and leads to adverse pregnancy outcomes (**Meena *et al.,* 2016**). Therefore, based on existing evidence and the results of various studies, it became essential to do more research on the correlation between the existence of anti-TPO Ab and adverse pregnancy outcome particularly in euthyroid women.

Though, the primary pathophysiology concerning the existence of anti-TPO antibodies with preterm labor is still under a scientific debate, several studies had proven that there is an association between anti-TPO Ab and preterm labor. In agreement with our results, *Masoomeh* and his colleagues reported also that females in with euthyroid state and tested positive for anti-TPO Ab were more prone to experience preterm labor 21% in comparison with pregnant females tested negative for anti-TPO Ab 4% (**Masoomeh *et al.,* 2019**). *Negro* and his colleagues reported the occurrence of preterm labor among anti-TPO negative females was 1.8% having a *P* value <0.01 and that the occurrence of preterm labor among pregnant females positive for anti-TPO Ab and females negative for this antibody was 22.4% vs. 8.2%, having a *P* value <0.01 (**Negro *et al.,* 2011; Chandaka *et al.,* 2022**). They assumed that thyroid mal function had a significant correlation with preterm labor and that anti-TPO Ab could be a strong marker of thyroid impartment. However, several studies did not find any correlation regarding presence of anti-TPO Ab and preterm labor (**Bryson *et al.,* 2003; Männistö *et al.,* 2010**).

In our study, pregnant females tested positive for anti-TPO Ab had preterm labor at a lower gestational age in comparison with controls. Which was in agreement with results of other studies, who reported that there is an association between anti-TPO Ab and preterm labor earlier than 34 weeks (**Masoomeh *et al.,* 2019**). Accordingly it is hypothized that pregnant females positive for anti-TPO Ab at are higher risk to go through preterm labor at lower gestational age in comparison to pregnant females who tested negative for anti-TPO Ab. In disagreement to our results several studies did not reach a correlation between pregnant females positive for anti-TPO Ab and preterm labor. *Toulis* and collegues had done an Australian study and detected no significant difference in occurence of preterm labor between females who were anti-TPO Ab positive against females who were anti-TPO Ab negative (**Toulis *et al.,* 2010**). The main reason for this disparity in our findings compared to other studies is mostly due to the sub grouping of preterm labor into spontaneous preterm labor and iatrogenic preterm labor done some other studies while we focused on preterm in general without sub grouping. Accordingly the existence of anti-TPO Ab among euthyroid pregnant females can be considered as a biomarker risk for preterm labor.

In our study there was no correlation between anemia tested in the first trimester and anti-TPO Ab. Scarce studies had investigated the association between anemia and thyroid disorders (**Leung *et al.,* 1993; Abalovich *et al.,* 2002**). Only a single study documented the correlation between the presence of anti-TPO Ab with maternal anemia (**Balucan *et al.,* 2013**). As in most of autoimmune cases, auto-antibodies might have a role in red blood cell destruction accompanied by sever auto inflammatory reactions. Also in our study, there was no significant difference observed in the incident of IUFD among studied groups, 7.5% among anti-TPO positive pregnant females and 5% among controls. Also we observed in our study, that IUGR did not occur in both studied groups as shown in table 2 despite the presence of anti-TPO Ab among pregnant females in the case group. In contrast to our results a study proved that TPO Ab postivty during pregnancy lead to have

a harmful impact on placentation for instance disturbing the normal primary and secondry Doppler pulse index in the uterus blood vessel, enhancing the threat of IUGR as well as gestatinal hypertension (**Beneventi *et al.,* 2022**). There was no difference documented in the occurrence of gestational hypertension between both studied groups, both recorded 5% occurrence. In disagreement to our results *Feki* and his colleagues stated that pregnant females with anti-TPO positivity have a higher tendency for acquiring gestational hypertension, recurrent abortions, as well as IUFD (**Feki *et al.,* 2008**) along with other studies (**Negro *et al.,* 2006; Meena and Nagar, 2016**). No statistically note Worth correlation among thyroid autoimmune disease and pregnancy-induced hypertension or gestational diabetes was found in our study. In agreement to our results, a study proved that there is no correlation regarding existence anti-TPO Ab and developing of gestational diabetes (GDM) during gestation period (**Plowden *et al.,* 2016; Erol *et al.,* 2022**). However in an Bangladesh they found out that AntiTPO Ab positive pregnant women face a higher risk of acquiring GDM; P <0.001 (**Sharmen *et al.,* 2022**).

We suggest that investigation of thyroid functions preferably to be done as early as possible during gestation and, if results are within normal range, investigations should be repeated 4 weeks after to confirm that there is the patient have not developed hypothyroidism. More studies are desired to explore pathophysiology of anti-TPO Ab with adverse pregnancy outcomes for better management of cases. And intake of levothyroxine among those females having subclinical hypothyroidism in the presence of anti-TPO Ab positivity should be explored.

LIMITATION

Our study is done to a referral fetal department in our institute. Patients from all over the country come here for prenatal counseling and follow up. However there are other few major hospitals where patients might be referred to as well. Therefore, the prevalence of anti-TPO positive results in the research we performed may not be reflective to the general population of the country.

CONCLUSION

In conclusion, even in pregnant women who are in a euthyroid state, thyroid autoimmune disorder is associated with poor pregnancy outcomes. Screening for thyroid autoimmunity among pregnant women might be of a clinical value as it allows early detection of pregnant women at risk. It appears sensible that these antibodies could serve as a potential early warning sign for unfavorable pregnancy outcomes linked to the thyroid. Also, it should be included in prenatal screening programs, tied with antepartum thyroxine supplementation for affected females, may even avoid certain unfavorable perinatal occurrences.

CONFLICT OF INTEREST

There are no conflicts of interest.

SOURCE OF FUNDING

This study was funded by me.

REFERENCES

Abalovich M. *et al.* (2002) 'Overt and subclinical hypothyroidism complicating pregnancy', Thyroid, 12(1), pp. 63–68. doi: 10.1089/105072502753451986.

Abalovich M. *et al.* (2013) 'Adequate levothyroxine doses for the treatment of hypothyroidism newly discovered during pregnancy', Thyroid, 23(11), pp.1479–1483. doi: 10.1089/thy.2013.0024.

Alijotas-Reig J. and Garrido-Gimenez C. (2013) 'Current concepts and new trends in the diagnosis and management of recurrent miscarriage', Obstetrical and Gynecological Survey. doi: 10.1097/OGX.0b013e31828aca19.

Andersen S.L. *et al.* (2018) 'Maternal Thyroid Function in Early Pregnancy and Child Neurodevelopmental Disorders: A Danish Nationwide Case-Cohort Study', Thyroid, 28(4), pp.537–546. doi: 10.1089/thy.2017.0425.

Bagis T., Gokcel A. and Saygili E.S. (2001) 'Autoimmune thyroid disease in pregnancy and the postpartum period: Relationship to spontaneous abortion', Thyroid, 11(11). doi: 10.1089/105072501753271743.

Balucan F.S., Morshed, S.A. and Davies T.F. (2013) 'Thyroid autoantibodies in pregnancy: Their role, regulation and clinical relevance', Journal of Thyroid Research. Hindawi Publishing Corporation, p.15. doi: 10.1155/2013/182472.

Beksac K. *et al.* (2022) 'Impact of anti-thyroid peroxidase and anti-thyroglobulin antibodies on the gestational outcome of euthyroid pregnancies: A retrospective study', Human Antibodies, 30(3), pp. 157–163. doi: 10.3233/HAB-220010.

Beneventi F. *et al.* (2022) 'Thyroid autoimmunity and adverse pregnancy outcomes: a prospective cohort study', Endocrine, 76(1), pp. 198–207. doi: 10.1007/s12020-021-02958-w.

Bryson C.L. *et al.* (2003) 'Association between Gestational Diabetes and Pregnancy-induced Hypertension', American Journal of Epidemiology. doi: 10.1093/aje/kwg273.

Chandaka H. *et al.* (2022) 'Study of prevalence of thyroid peroxidase antibodies in preterm deliveries and recurrent pregnancy loss', International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 11(11), p.3142. doi: 10.18203/2320-1770.ijrcog20222810.

Chardès T. *et al.* (2002) 'The human anti-thyroid peroxidase autoantibody repertoire in Graves' and Hashimoto's autoimmune thyroid diseases', Immunogenetics, pp.141–157. doi: 10.1007/s00251-002-0453-9.

Chen X. *et al.* (2022) 'Iodine nutrition status and thyroid autoimmunity during pregnancy: a cross-sectional study of 4635 pregnant women', Nutrition Journal, 21(1). doi: 10.1186/s12937-022-00760-6.

Cleary-Goldman J. *et al.* (2008) 'Maternal thyroid hypofunction and pregnancy outcome', Obstetrics and Gynecology, 112(1). doi: 10.1097/AOG.0b013e3181788dd7.

Dhillon-Smith R.K. and Coomarasamy A. (2020) 'TPO antibody positivity and adverse pregnancy outcomes', Best Practice and Research: Clinical Endocrinology and Metabolism. doi: 10.1016/j.beem.2020.101433.

Van Dijk M.M. *et al.* (2022) 'Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial', The Lancet Diabetes and Endocrinology, 10(5), pp.322–329. doi: 10.1016/S2213-8587(22)00045-6.

Dong A.C. *et al.* (2020) 'Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis', Fertility and Sterility, 113(3), pp.587-600.e1. doi: 10.1016/j.fertnstert.2019.11.003.

Erol S.A. *et al.* (2022) 'Evaluation of Perinatal and Neonatal Outcomes in Pregnant Women with Thyroid Autoantibody Positivity (Anti-thyroglobulin and Anti-thyroid Peroxidase) Due to Thyroiditis', SN Comprehensive Clinical Medicine, 4(1). doi: 10.1007/s42399-022-01151-y.

Feki M. *et al.* (2008) 'Thyroid disorders in pregnancy: Frequency and association with selected diseases and obstetrical complications in Tunisian women', Clinical Biochemistry, 41(12), pp.927–931. doi: 10.1016/j.clinbiochem.2008.05.002.

Gameil M.A. *et al.* (2023) 'Influence of thyroid autoimmunity at various clinical stages of hypothyroidism on the risk of miscarriage before 20 weeks of gestation', Hormones, 22(4), pp.587–593. doi: 10.1007/s42000-023-00474-2.

Ghalib H.A., Fattah C.N. and Mohammed A.K. (2023) 'Association between antithyroid peroxidase antibody and recurrent miscarriage', European Review for Medical and Pharmacological Sciences, 27(7), pp.3003–3008. doi: 10.26355/eurrev_202304_31933.

Glinoer H. (2011) 'Personal Considerations on the 2011 American Thyroid Association and the 2007 Endocrine Society Pregnancy and Thyroid Disease Guidelines', Thyroid, 21(10). doi :10.1089/thy.2011.2110.ed2.

Hollowell J.G. *et al.* (2002) 'Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III)', Journal of Clinical Endocrinology and Metabolism, 87(2), pp.489–499. doi: 10.1210/jcem.87.2.8182.

Jonklaas J. *et al.* (2014) 'Guidelines for the treatment of hypothyroidism: Prepared by the American thyroid association task force on thyroid hormone replacement', Thyroid, 24(12), pp.1670–1751. doi: 10.1089/thy.2014.0028.

Karakosta P. *et al.* (2012) 'Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes', The Journal of clinical endocrinology and metabolism, 97(12), pp.4464–4472. doi: 10.1210/JC.2012-2540.

Kyrilli A., Unuane D., Poppe K.G. (2023) 'Thyroid autoimmunity and pregnancy in euthyroid women', Best Practice and Research: Clinical Endocrinology and Metabolism. doi: 10.1016/j.beem.2022.101632.

Leung A.S. *et al.* (1993) 'Perinatal outcome in hypothyroid pregnancies', Obstetrics and Gynecology, 81(3), pp.349–353. doi: 10.1016/0020-7292(93)90343-u.

Li G. *et al.* (2022) 'Effect of Levothyroxine on Pregnancy Outcomes in Pregnant Women With Hypothyroxinemia: An Interventional Study', Frontiers in Endocrinology, 13. doi: 10.3389/fendo.2022.874975.

Liu M. *et al.* (2022) 'Association of thyroid peroxidase antibodies with the rate of first-trimester miscarriage in euthyroid women with unexplained recurrent spontaneous abortion', Frontiers in Endocrinology, 13. doi: 10.3389/fendo.2022.966565.

Männistö T. *et al.* (2010) 'Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life', Journal of Clinical Endocrinology and Metabolism, 95(3), pp.1084–1094. doi: 10.1210/jc.2009-1904.

Masoomeh M. *et al.* (2019) 'Effect of antithyroid peroxidase antibody on pregnancy outcome in euthyroid women', Perinatology, 20(1), pp.10–15.

McElduff A. and Morris J. (2008) 'Thyroid function tests and thyroid autoantibodies in an unselected population of women undergoing first trimester screening for aneuploidy', Australian and New Zealand Journal of Obstetrics and Gynaecology, 48(5). doi: 10.1111/j.1479-828X.2008.00903.x.

Meena A. and Nagar P. (2016) 'Pregnancy Outcome in Euthyroid Women with Anti-Thyroid Peroxidase Antibodies', Journal of Obstetrics and Gynecology of India, 66(3), pp.160–165. doi: 10.1007/s13224-014-0657-6.

Meena M. *et al.* (2016) 'The effect of anti-thyroid peroxidase antibodies on pregnancy outcomes in euthyroid women', Journal of Clinical and Diagnostic Research, 10(9), pp.QC04–QC07. doi: 10.7860/JCDR/2016/19009.8403.

Mooradian A.D. (2023) 'Age-related thyroid hormone resistance: A friend or foe', Endocrine and Metabolic Science. doi: 10.1016/j.endmts.2023.100132.

Mumusoglu S. *et al.* (2016) 'Does the presence of autoantibodies without autoimmune diseases and hereditary thrombophilia have an effect on recurrent pregnancy loss?', Journal of Maternal-Fetal and Neonatal Medicine, 29(14), pp.2352–2357. doi: 10.3109/14767058.2015.1085964.

Negro R. *et al.* (2006) 'Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: Effects on obstetrical complications', Journal of Clinical Endocrinology and Metabolism, 91(7), pp.2587–2591. doi: 10.1210/jc.2005-1603.

Negro R. *et al.* (2011) 'Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes', Journal of Clinical Endocrinology and Metabolism, 96(6). doi: 10.1210/jc.2011-0026.

Netra H.K., Pant R., Banerjee K.P. (2020) 'An observational study of fetomaternal outcome in euthyroid women with anti-thyroid peroxidase antibodies at tertiary care hospital', International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 9(6), p.2476. doi: 10.18203/2320-1770.ijrcog20202332.

Plowden T.C. *et al.* (2016) 'Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss, or live birth', Journal of Clinical Endocrinology and Metabolism, 101(6), pp.2358–2365. doi: 10.1210/jc.2016-1049.

Poppe K., Velkeniers B., Glinoer D. (2008) 'The role of thyroid autoimmunity in fertility and pregnancy', Nature Clinical Practice Endocrinology and Metabolism, pp.394–405. doi: 10.1038/ncpendmet0846.

Rajput R. *et al.* (2017) 'Prevalence of thyroid peroxidase antibody and pregnancy outcome in euthyroid autoimmune positive pregnant women from a tertiary care center in Haryana', Indian Journal of Endocrinology and Metabolism, 21(4), pp.577–580. doi: 10.4103/ijem.IJEM_397_16.

Seungdamrong A. *et al.* (2017) 'Preconceptional antithyroid peroxidase antibodies, but not thyroid-stimulating hormone, are associated with decreased live birth rates in infertile women', Fertility and Sterility, 108(5), pp.843–850. doi: 10.1016/j.fertnstert.2017.08.026.

Sharmen F. *et al.* (2022) 'Increased occurrence of hypothyroidism among pregnant women during the first trimester and its correlation with anti-thyroid peroxidase antibody (anti-TPO) and gestational diabetes mellitus in Chattagram region, Bangladesh', International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 12(1), p.58. doi: 10.18203/2320-1770.ijrcog20223475.

Stagnaro-Green A. *et al.* (1990) 'Detection of At-Risk Pregnancy by Means of Highly Sensitive Assays for Thyroid Autoantibodies', JAMA: The Journal of the American Medical Association, 264(11). doi: 10.1001/jama.1990.03450110068029.

Stricker Reto *et al.* (2007) 'Evaluation of maternal thyroid function during pregnancy: The importance of using gestational age-specific reference intervals', European Journal of Endocrinology, 157(4), pp.509–514. doi: 10.1530/EJE-07-0249.

Surks M.I. and Hollowell J.G. (2007) 'Age-specific distribution of serum thyrotropin and antithyroid antibodies in the U.S. population: Implications for the prevalence of subclinical hypothyroidism', Journal of Clinical Endocrinology and Metabolism, 92(12), pp.4575–4582. doi: 10.1210/jc.2007-1499.

Tanacan A. *et al.* (2019) 'Impact of extractable nuclear antigen, anti-double stranded DNA, antiphospholipid antibody, and anticardiolipin antibody positivity on obstetrical complications and pregnancy outcomes', Human Antibodies, 27(2), pp.135–141. doi: 10.3233/HAB-180359.

Tańska K. *et al.* (2023) 'Thyroid autoimmunity and its negative impact on female fertility and maternal pregnancy outcomes', Frontiers in Endocrinology. doi: 10.3389/fendo.2022.1049665.

Thangaratinam S. *et al.* (2011) 'Association between thyroid autoantibodies and miscarriage and preterm birth: Meta-analysis of evidence', BMJ, 342(7806). doi: 10.1136/bmj.d2616.

Toulis K.A. *et al.* (2010) 'Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: A meta-analysis', European Journal of Endocrinology, pp.643–652. doi: 10.1530/EJE-09-0850.

Trbojević B. and Djurica S. (2005) 'Diagnosis of autoimmune thyroid disease', Srpski arhiv za celokupno lekarstvo, pp.25–33. doi: 10.2298/SARH05S1025T.

Ünal C., Fadiloglu E., Beksac M.S. (2019) 'Pregnancy outcomes of the patients with anti-smooth muscle antibody positivity', Human Antibodies, 27(3), pp.167–170. doi: 10.3233/HAB-190365.

Vargatu I. (2016) 'Williams Textbook of Endocrinology', Acta Endocrinologica (Bucharest), 12(1), pp.113–113. doi: 10.4183/aeb.2016.113.

Vissenberg R. *et al.* (2016) 'Live-birth rate in euthyroid women with recurrent miscarriage and thyroid peroxidase antibodies', Gynecological Endocrinology, 32(2), pp.132–135. doi: 10.3109/09513590.2015.1092513.

Xu Y. *et al.* (2023) 'Thyroid autoimmunity and adverse pregnancy outcomes: A multiple center retrospective study', Frontiers in Endocrinology, 14. doi: 10.3389/fendo.2023.1081851.

Zhang S. *et al.* (2023) 'High level of thyroid peroxidase antibodies as a detrimental risk of pregnancy outcomes in euthyroid women undergoing ART: A meta-analysis', Molecular Reproduction and Development, pp. 218–226. doi: 10.1002/mrd.23677.