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Effect of Antithyroid Peroxidase Antibody on Pregnancy Outcome in Euthyroid Women

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Abstract

Background: Antithyroidperoxidase (anti-TPO) antibodies can have an adverse effect on pregnancy outcomes. The presence of these antibodies is associated with pregnancy complications such as preterm labor, macrosomia, and spontaneous miscarriage in euthyroid women. However, less is known about thyroid antibodies and their relationship with pregnancy complications.

Aim: To determine the relationship between anti-TPO antibodies and preterm labor, macrosomia, and spontaneous miscarriage in euthyroid pregnant women

Materials and Methods: This was a prospective study conducted on all the pregnant women who were referred to Mahdiyeh Hospital (Tehran, Iran) from 2014 to 2016. One hundred pregnant women with anti-TPO antibodies detected in their blood were chosen as the case group and 300 pregnant women without this antibody were chosen as the control group. The relationship between anti-TPO antibodies and preterm labor, macrosomia, and spontaneous miscarriage was studied.

Results: Of the study population, 21% with anti-TPO antibodies and 3.7% without this antibody had preterm labor. In the control group, 5.7% had spontaneous miscarriage, while 19% in the case group had spontaneous miscarriage. Regarding the occurrence of macrosomia, the difference between the case and control groups was not significant (P = .069).

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Conclusion: Anti-TPO antibodies have no effect on the incidence of gestational diabetes mellitus, and therefore they do not have a significant effect on macrosomia. Despite these hypotheses, more studies analyzing the association between macrosomia and anti-TPO antibodies, with a larger statistical population, are needed.

Key Words: Antithyroid peroxidase antibody, pregnancy outcome, macrosomia, preterm labor, spontaneous miscarriage

Introduction

Thyroid disorders, especially autoimmune types, are common in women in reproductive ages. About 4% of women in their reproductive age have positive titers of antithyroid peroxidase (anti-TPO) antibodies or thyroglobulin antibody.[1,2] Recent studies have proven that thyroid disorders during pregnancy can increase the risk of pregnancy complications such as preterm labor, placental abruption, intrauterine fetal death, preeclampsia, and neuropsychologic developmental disorders.[3-7] Some evidence determines that high levels of antithyroid antibodies, especially anti-TPO antibodies, in pregnant women (even in euthyroid women) are associated with an increased risk of spontaneous miscarriage and preterm labor[8]; the risk of preterm labor,[9,10] spontaneous miscarriage,[11] placental abruption,[12] postpartum thyroiditis, and postpartum depression is higher in these women.[13] In addition, it has been reported that a rise in the level of thyroid-stimulating hormone (TSH), even within the normal range of nonpregnant women, is associated with an increased risk of delivering large-for-gestational-age neonates, and this risk is even higher in women who are positive for anti-TPO antibodies.[14]

Anti-TPO antibodies are seen in 18.9% of women in their reproductive age.[15] In some of the studies, it has been proven that 17% to 33% of women with a history of recurrent spontaneous miscarriage had a higher anti-TPO antibody level compared with normal women. Also, in women who had a history of infertility, it is possible that the anti-TPO antibody level is 10% to 31% higher than in other pregnant women.[7] A prospective study showed that the neonatal mortality rate in women who were positive for anti-TPO antibodies was 2 to 3 times higher than in women without this antibody. It seems that a part of this issue can be because of the increase in the incidence of preterm labor, which is caused after the increase in the level of anti-TPO antibodies.[16] In a randomized, controlled clinical trial, it was shown that in euthyroid women with anti-TPO antibodies who were treated with levothyroxine during pregnancy, the rate of spontaneous miscarriage and preterm labor was less compared with women who received the placebo. Presence of levothyroxine antibodies, even in the absence of obvious thyroid function disorder, can lead to a 3 to 5 times increased danger of spontaneous miscarriage and preterm labor.[15,17,18]

According to the American Thyroid Association's 2011 Guidelines, there is not enough evidence to support or deny performing a general screening for the presence of anti-TPO antibodies in pregnant women or treating anti-TPO antibody–positive euthyroid women with levothyroxine.[19] Therefore, based on existing evidence and the results of various studies, it seems necessary to conduct further studies on the relationship between the presence of anti-TPO antibodies and the side effects in pregnancy, including preterm labor, especially in euthyroid women.

Aim

To analyze the association between the presence of anti-TPO antibodies in euthyroid pregnant women and the incidence of preterm labor in them

Materials and Methods

Study design

This prospective cohort study was conducted in Mahdiyeh Hospital (Tehran, Iran) affiliated to Shahid

Beheshti University (Tehran, Iran) from 2014 to 2015. Overall, 5000 pregnant women who visited the gynecology ward were screened.

Study population

Of the 5000 pregnant women screened, those positive for anti-TPO antibodies (n = 100; 2% of the pregnant population) were included in the case group. To serve as controls, 300 pregnant women without this antibody were selected by simple random sampling of the pregnant population. The exclusion criteria were as follows: age, older than 40 or younger than 18 years; short cervical length; either presence or history of spontaneous miscarriage or preterm labor, cervical surgery, sexually transmitted diseases, bacteriuria, systemic infections (pyelonephritis, pneumonia, and appendicitis), placenta previa, placental abruption, cigarette smoking, uterine anomalies, vaginal bleeding (especially > 1 trimester), intrauterine growth retardation, and fetal anomaly; clinical evidence of thyroid dysfunction (such as goiter); use of immunosuppressants; anemia (hemoglobin level < 10 g/dL); family history of preterm labor, diabetes, and obesity (BMI > 30); TSH level above normal, which was checked until the 13th week of pregnancy (in our medical center, TSH level > 40 is considered positive); low TSH level (< 5.5); and high free T4 level (after checking for TSH level, using ultrasensitive methods). In general, all women with a normal TSH level (0.5 to 8, euthyroid women) were taken for the study.

At the end of pregnancy, the considered complications, namely, preterm labor, spontaneous miscarriage, and macrosomia were analyzed.

The institutional ethical body's approval was obtained. All women in the case group signed the informed consent before entering the study. This study had been approved by the Shahid Beheshti University of Medical Sciences and Health Services' review board.

Study procedure

From both the groups, risk factors including age; BMI; parity; and history of preterm delivery, spontaneous miscarriage, and macrosomia (birth weight > 4500 g) were collected. Then, anti-TPO antibody serum level was checked using the ELISA method in both the cases and controls. TSH level was measured in all pregnant women until the 13th week of pregnancy using Monobind kit (CA, USA).

Statistical analysis

T test and Chi square test were used to compare the data, and SPSS software version 21 (IBM, Armonk, NY, USA) was used to analyze the data.

Results

There were 100 participants (average age = 26.7 y) in the case group and 300 participants (average age = 27.6 y) in the control group. There were no significant differences between both the groups regarding maternal age variables, BMI, and parity (P > .05; Table 1). In both the groups, the mean age was not statistically significant (P = .4).

Of the 300 pregnant women in the control group (anti-TPO antibody negative), 11 (3.7%) had preterm labor, while 21 (21%) of the 100 pregnant women in the case group (anti-TPO antibody positive) had preterm labor

Table 1. Parameters Documented in the 2 Groups

Parameter	Case Group	Control Group
Maternal Age, y	26.7	27.6
BMI	25.8	25.4
Parity	1.71	1.36
Gestational Diabetes	2 of 3 cases	Both the cases

Table 2. Distribution of Preterm Delivery, Spontaneous Miscarriage, and Macrosomia Variables in the 2 Groups

Parameter	Occurred/Did Not Occur	Anti-TPO Antibody Status		P Value
		Negative, n (%)	Positive, n (%)	
Preterm Delivery	Occurred	11 (3.7)	21 (21)	< .001
	Did not occur	289 (96.3)	79 (79)	
Spontaneous Miscarriage	Occurred	17 (5.7)	19 (19)	< .001
	Did not occur	283 (94.3)	81 (81)	
Macrosomia	Occurred	2 (0.7)	3 (3)	< .001
	Did not occur	298 (99.3)	97 (97)	

Anti-TPO antibody, anti-thyroid peroxidase antibodies.

(Table 2). The incidence of preterm labor between the 2 groups was statistically significantly different ($P < .005$) based on the Chi square test. Based on the OR (odds ratio), the chances of preterm delivery in the case group was 13.23 times higher than in the control group (95% CI: 29.26; OR = 2). The mean gestational age in women in the control group who had preterm delivery was 35.7 weeks, and in the control group women, it was 31.3 weeks; this difference was statistically significant ($P < .005$). The highest preterm birth rates in the case group occurred at a gestational age of 32 to 33 weeks, while in the control group, it occurred at gestational age of 34 to 36 weeks.

Based on the results, in the case group, the highest incidence of spontaneous preterm delivery was 78.9%, and the incidence of preterm delivery related to premature rupture of membranes was 21.1%. In the control group, the respective incidences were 70% and 70% (Table 3).

Of the 300 pregnant women in the control group, 17 (5.7%) had spontaneous miscarriage (mean age, 28.8 y). Of the 100 pregnant women in the case group, 19 (19%) had spontaneous miscarriage (mean age, 29.1 y), which was statistically significant according to Chi square test ($P < .001$; Table 2). Based on the OR, the chances of spontaneous miscarriage in the case group was 3.9 times higher than in the control group (95% CI: 1.94–8.86). Both the groups had the highest spontaneous miscarriage rates in pregnant women between 35 and 40 years of age, and the highest spontaneous miscarriage rates occurred in the second trimester. Of the 19 pregnant women who had spontaneous miscarriage in the case group, 7 (36.9%) were in their first trimester and 12 (63.1%) were in their second trimester.

Table 3. Causes of Preterm Delivery in the 2 Groups

Cause of Preterm Delivery	Case Group	Control Group
Spontaneous Preterm Delivery, %	78.9	70
Premature Rupture of Membranes, %	21.1	70

The incidence of macrosomia was lower in the control group (0.7%) than in the case group (3%), but this difference was not statistically significant.

Discussion

In this study, the role of anti-TPO antibodies as one of the antithyroid antibodies in the incidence of pregnancy complications including spontaneous miscarriage, preterm labor, and macrosomia was investigated. Based on the results of this study, euthyroid pregnant women with anti-TPO antibody positivity were more likely to go through preterm labor compared with pregnant women without this antibody (21% vs 4%).

In most studies, similar results are obtained. For example, in a study, the prevalence of very preterm delivery in women with anti-TPO antibody positivity was 4.5%, and in women without this antibody, it was 1.8% ($P < .01$), which is similar to the results of our study.[20] It seems that the reason behind these results is thyroid dysfunction, which has a proven role in early delivery, and anti-TPO antibody positivity is a marker of thyroid dysfunction. Also, in that study, the prevalence of preterm labor in pregnant women with anti-TPO antibody positivity and women without this antibody was 22.4% and 8.2%, respectively ($P < .01$).[20] In our study, pregnant women with anti-TPO antibody positivity had preterm labor at a lower gestational age, which is consistent with results of Dr Aruna Meena, who states that there is a relationship between anti-TPO antibodies and preterm delivery before 34 weeks. Therefore, it can be concluded that the risk of preterm delivery in pregnant women with anti-TPO antibody positivity at lower gestational ages is higher than in pregnant women who are negative for anti-TPO antibodies. Also, as the gestational age increases, the risk of preterm labor was not different in the 2 groups.

On the other hand, some of the studies were not able to find a relationship between preterm labor and anti-TPO antibodies. Perhaps the reason for the difference in our results with this series of articles is because of the classification of preterm labor into spontaneous preterm labor and iatrogenic preterm labor. In general, it seems that although the underlying mechanism of the association between anti-TPO antibodies with early delivery is

not known, some studies have shown the relationship between anti-TPO antibodies and preterm labor; therefore, the presence of anti-TPO antibodies in euthyroid pregnant women can be considered as a risk factor for early delivery.

Also, the incidence of spontaneous miscarriage was significantly higher in anti-TPO antibody–positive women than in anti-TPO antibody–negative women (19% vs 6%; $P < .001$). In a study, the reason was explained as an association with anticardiolipin antibody,[13] while other studies have suggested antithyroid agents as an independent factor in spontaneous miscarriage and recurrent spontaneous miscarriages.

Although our study proved that the incidence of macrosomia in euthyroid pregnant women with anti-TPO antibody positivity is higher than in pregnant women without this antibody (0.3% vs 0.7%), this difference was not statistically significant. However, at the universal level, there have not been many studies on the effect of antithyroid antibodies on incidence of macrosomia in newborns. A study by Männistö et al,[21] in 2009, had similar results to our study. In that study, the incidence of macrosomia in euthyroid pregnant women with anti-TPO antibody positivity was higher than in pregnant women without this antibody (2.4% vs 0.8%); however, the difference was not statistically significant ($P = .017$).

Although there is evidence for a relation between the presence of anti-TPO antibodies and additional risk of pregnancy adverse effects, the results of studies on the use of levothyroxine in euthyroid women with underlying autoimmunity are currently awaited. Hence, further trials have to be designed for defining women who require levothyroxine replacement and to determine the advantages of a predictive dose-adjustment strategy.[14,22]

Considering our study on anti-TPO antibodies and TSH hormone level and the chance of hypothyroidism in pregnancy, further studies are suggested to investigate the rate of pregnancy complications and anti-TPO antibodies and TSH hormone level.

Conclusion

With regard to studies on the relationship between gestational diabetes mellitus as a risk factor for macrosomia and the presence of anti-TPO antibodies, it can be concluded that anti-TPO antibodies have no effect on the incidence of gestational diabetes mellitus, and therefore it does not have a significant effect on macrosomia. Despite these hypotheses, more studies are needed on the association between macrosomia and antithyroid antibodies with a larger statistical population.

Future studies are recommended to focus on the efficacy of levothyroxine therapy on reducing the complications of antithyroid antibodies (especially spontaneous miscarriage and early delivery). If the effectiveness of levothyroxine in reducing the number of spontaneous miscarriages and preterm delivery in pregnant women with antithyroid antibodies is proved, an algorithm for screening and treating pregnant women should be provided.

The main strength of our study is reconciling the 2 groups in terms of risk factors for preterm labor. This issue was less noticeable in other studies. One of the limitations of our study is the number of examined samples.

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