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Original Article

An investigation into thyroid function tests in pregnant women and the relationship between thyroid autoantibodies and preeclampsia

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Abstract

Aim: Preeclampsia and eclampsia which can be seen during the last trimester of pregnancy prove to be significant pregnancy complications whose physiopathology still remains unclear. Available data demonstrate that disorders of the thyroid hormone may possibly alter the progress of pregnancy. The aim of this study was to investigate the relationship between thyroid antibodies and preeclampsia development.

Materials and Methods: This retrospective study is a total of 216 cases were included in the study out of which 72 were pregnant women with preeclampsia who had been followed-up at University of Medical Sciences, Adana City Hospital, Obstetrics and Gynecology Clinic, 72 were healthy pregnant women followed-up at the same clinic, and 72 healthy non-pregnant women but had presented to the internal medicine clinic for various reasons. Statistical analyses of the comparisons of the thyroid tests and thyroid autoantibodies among the all three groups were conducted as well.

Results: 45 of the patients with preeclampsia had mild preeclampsia, while 27 had severe preeclampsia. While no significant difference was found among pregnant women with preeclampsia, healthy pregnant women, and the control groups with regards to the Thyroid Stimulating Hormone (TSH) values as revealed by intergroup and intragroup comparisons for multiple groups, the free triiyodotironin(fT3) and free tetraiyodotironin (fT4) values were found to be significantly lower in the preeclampsia and healthy pregnant groups at an advanced level than the control group statistically ($p<0.001$). The anti-TPO titer of the patients with preeclampsia was found to be significantly higher than that of the healthy pregnant women ($p=0.038$). There was also no significant difference among the groups when the groups were compared as to the thyroid autoantibody positivity and negativity ($p> 0.005$).

Conclusion: The results of our study revealed that the alterations seen in thyroid hormones might pose a risk for preeclampsia development but autoantibodies were not sufficient enough to bring about preeclampsia development.

Keywords: Hypertension; preeclampsia; pregnancy; thyroid autoantibody

INTRODUCTION

The rate of disorders of the thyroid gland that are frequently seen in women in their reproductive age may increase in the gestational period and the existent diseases of the thyroid may negatively affect the progress of pregnancy (1). Alterations are especially seen in Thyroid Stimulating Hormone (TSH) and free tetraiyodotironin (fT4) during pregnancy. While free triiyodotironin(fT3) gradually decreases during pregnancy, TSH levels are elevated but T4 levels decrease as opposed to the fact that TSH is low and T4 is high at the beginning (2). Studies have shown that antithyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG), among the thyroid autoantibodies, were risk factors for fetal losses (3,4).

Preeclampsia is a significant complication of pregnancy emerging after the 20th week of pregnancy which is characterized by proteinuria and hypertension thereby posing a danger for the mother and the fetus (5, 6). Multiple factors like metabolic and cardiovascular risk factors constituting predisposition with the partial contribution of systemic inflammation may play a role in its pathology (7). In spite of the presence of an ample number of studies that have been conducted for many years, the etiopathogenesis of preeclampsia has not been fully unraveled. Therefore, the sole effective treatment is the induction of labor (8). When the risks that preeclampsia would bring about for both the mother and the fetus are taken into consideration, the risks that might cause preeclampsia still prove to be a matter of interest for researchers.

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Thus, the aim of our study was to investigate the relationship between preeclampsia, which is an important complication of pregnancy, and diseases of the thyroid and autoantibodies which give way to various complications frequently seen in pregnant women.

MATERIAL and METHODS

This retrospective study is a total of 216 cases were included in the study out of which 72 were last trimester pregnant women with preeclampsia who had presented to the University of Medical Sciences, Adana Numune Health Practices and Research Hospital, Obstetrics and Gynecology Clinic between 2013 and 2016, 72 were healthy last trimester pregnant women who had presented to the same clinic at the same time interval, and 72 healthy non-pregnant women who had presented to the internal medicine clinic for various reasons. While the patients with preeclampsia were allocated to the study group, healthy pregnant and non-pregnant women were allocated to the control group. The demographic characteristics, blood values, and physical examination results were obtained retrospectively through the review of patients' files.

Patients with preeclampsia were classified as those with severe and mild preeclampsia according to the criteria set by the National High Blood Pressure Education Program Working Group (9). The laboratory analyses of all the cases had been carried out at our hospital's biochemistry laboratory. The TSH, free T3, T4, and anti-thyroglobulin values were analyzed by immunoassay method with the Roche Cobas 8000 analyzer.

Exclusion criteria for the study group were established as the existence of such diseases as hypertension, thyroid disease, chronic or acute hepatic disease, and coronary disease, administration of drugs that would affect thyroid functions, and previous history of thyroid operations.

Board of Ethics

The study was found to be in accordance with ethics of research with the unanimous vote of the board members at the 58th meeting of the Çukurova University Medical School's Board of Ethics for Non-Invasive Clinical Research held on November 4, 2016.

Statistical analysis

The statistical analyses of the data collected within the scope of the study were conducted by IBM SPSS 20 package software (IBM SPSS Statistics 20 Inc., Chicago. USA). The Shapiro-Wilk test was utilized for data's competence to the normality hypothesis. The constant variables in descriptive statistics were signified by mean ± standard deviation, median, and minimum-maximum values, while the categorical variables were stated by the number of subjects and in percentages. The Mann-Whitney U test was used in the comparisons between two groups, while the Kruskall-Wallis H test with Benferoni correction and one-way analysis of variance (ANOVA) were utilized for the comparisons of three or more groups alongside with the post-hoc utilization of Tukey's HSD test for the establishment of differences among the groups. Dependency among the variables was analyzed by the chi-square and Fisher's exact test. Correlation analysis was conducted for anti-TPO and anti-TG levels using Spearman's rho. A multiple linear regression model was constructed for the TSH, T3, T4, anti-TPO, and anti-TG levels. The results were summarized in tables and graphs. While 0.05 was set as the statistical significance level, in cases where the results signify $p<0.05$ it was stated that there was a statistically significant difference and in cases where the results signify $p>0.05$ it was noted that there was no significant difference.

RESULTS

Out of a total of 72 patients covered by the study 45 patients had mild preeclampsia, while 27 had severe preeclampsia. The demographic characteristics and laboratory results of the groups are presented in Table 1.

Table 1. Descriptive statistics of the groups' demographic characteristics and laboratory results

Variable*	Preeclampsia (n=72)	Mild Preeclampsia (n=45)	Severe Preeclampsia (n=27)	Healthy Pregnant (n=72)	Control (n=72)
Age	29.1±6.3	28.5±6.2	30.3±6.4	27.1±6.8	27.9±6.9
Gravida	3 (0-12)	3 (0-7)	3 (1-12)	2 (1-11)	-
Parity	2 (0-10)	1 (0-5)	2 (0-10)	1 (0-10)	-
Abortus	0 (0-3)	0 (0-3)	0 (0-2)	0 (0-5)	-
Stillbirth	0 (0-3)	0 (0-1)	0 (0-3)	0 (0-1)	-
Curettage	0 (0-1)	0 (0-1)	0	0 (0-1)	-
Living	2 (0-9)	1 (0-5)	2 (0-9)	1 (0-10)	-
TSH	2.3±1.4	2.4±1.4	2.2±1.3	2.3±1.2	1.9±1.1
T3	2.4±0.6	2.6±0.6	2.3±0.6	2.6±0.5	3.2±0.5
T4	0.9±0.2	0.9±0.2	0.9±0.1	0.9±0.2	1.2±0.2
Anti-tpo	12.3±16.7	11.7±14.7	13.4±20.1	9.7±13.1	11.2±12.8

Anti-tg	15.6±21.4	13.4±10.6	19.3±32.2	11.7±5.9	20.3±47.5
Ta Systolic	158.3±13.8	149.0±4.8	173.7±9.5	106.1±8.9	110.2±11.1
Ta diastolic	93.4±10.1	90.7±6.8	97.9±12.8	68.8±8.2	67.5±7.6
ALT	18.1±20.1	15.8±11.9	21.9±28.8	11.0±4.3	17.5±9.1
AST	26.7±20.2	23.4±9.9	32.3±29.8	20.9±9.6	17.2±6.4
Platelet	232597.2±81715.3	230955.5±62471.1	235333.3±107784.6	259847.2±222829.5	298375±88481.8
Creatine	0.6±0.2	0.6±0.2	0.6±0.2	0.5±0.1	0.5±0.1
Pulmonary edema	0	0	0	-	-
Cyanosis	0	0	0	-	-
Headache	1(0-1)	1 (0-1)	1 (0-1)	-	-
Visual impairment	0 (0-1)	0 (0-1)	1 (0-1)	-	-
Mental disorder	0 (0-1)	0 (0-1)	1 (0-1)	-	-

*Summarized in terms of mean±sd, median (min-max), n (%). Anti-TPO:Antithyroid Peroxidase, Anti-TG: Antithyroglobulin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase

While no statistically significant difference could be found among the pregnant patients with preeclampsia, healthy pregnant women and the control groups with regards to TSH values as revealed by the results of intergroup and intragroup comparisons carried out for multiple groups, free T3 and free T4 values were found to be significantly lower at an advanced degree in the preeclampsia and healthy pregnant groups than those of the control group statistically ($p<0.001$). The mean free T3 and free T4 values of the preeclampsia and the healthy pregnant groups were found to be lower than those of the control group (Table 2).

When the patients with preeclampsia were compared to the control groups with regards to autoantibodies, it was found that the anti-TPO titer was significantly higher in the preeclampsia group than that of the healthy pregnant group ($p=0.038$) (Table 3).

Table 2. Multiple comparisons of TSH, free T3, free T4 values among the groups

Variable*	Patient (n=72)	Pregnant (n=72)	Control (n=72)	P	
TSH	2.3±1.4 (0.3-6.6)	2.3±1.2 (0.4-7.7)	1.9±1.1 (0.4-5.6)	Patient-Pregnant	0.997
				Patient-Control	0.149
				Pregnant-Control	0.170
T3	2.5±0.6 (0.8-4.2)	2.6±0.5 (1.5-3.7)	3.2±0.5 (1.0-4.1)	Patient-Pregnant	0.602
				Patient-Control	**<0.001**
				Pregnant-Control	**<0.001**
T4	0.9±0.2 (0.7-1.4)	0.9±0.2 (0.7-1.7)	1.2±0.2 (0.9-2.6)	Patient-Pregnant	0.547
				Patient-Control	**<0.001**
				Pregnant-Control	**<0.001**

*Summarized in terms of mean±sd, (min-max). TSH: Thyroid Stimulating Hormone

Table 3. Paired comparisons of antibody titers with preeclampsia and the groups

	Patient (n=72)		Pregnant (n=72)		Control (n=72)		P	
	Median (Min-Max)	Mean Rank	Median (Min-Max)	Mean Rank	Median (Min-Max)	Mean Rank		
Anti-TPO titer	8 (4-102)	115.9	7 (4-99)	94.8	8 (4-93)	114.7	Patient-Pregnant	**0.038**
							Patient-Control	0.568
Anti-TG titer	9 (9-152)	101.7	9 (9-47)	106.6	10 (9-392)	117.3	Patient-Pregnant	0.922
							Patient-Control	0.104

Anti-TPO: Antithyroid Peroxidase, Anti-TG: Antithyroglobulin

No significant differences, however, were found among the groups regarding the comparison of thyroid autoantibody positivity and negativity among the groups ($p > 0.005$). Moreover, it was not found to be related to the severity of preeclampsia either.

DISCUSSION

While pregnancy changes the course of some autoantibody positive diseases like lupus and rheumatoid arthritis, some autoantibody positive diseases like the antiphospholipid syndrome may alter the progress of pregnancy. On the one hand, while the effects of thyroid hormones on the formation and development of pregnancy are very well-known, on the other hand, the effects of euthyroid autoimmune thyroid diseases which are commonly seen still prove to be controversial. Moreover, there is only a limited number of studies on both the development and course of preeclampsia, which especially appears as an important complication of pregnancy in the late pregnancy period, and thyroid hormones alongside with antibodies.

The results of our study, in which we aimed to compare the results of thyroid function tests and thyroid autoantibodies in preeclamptic pregnant patients, healthy pregnant women, and healthy women, revealed that the anti-TPO titer that is listed among the thyroid autoantibodies in preeclamptic pregnant patients was significantly higher than that of the other groups.

Recently studies, which have investigated the relationship between thyroid autoantibody positivity and the severity of preeclampsia in various ethnic groups, have gained momentum. In a study by Elhaj et al. conducted with Sudanese women, the authors have reported that while the anti-TPO antibodies in preeclamptic women were significantly higher, there was no relationship between them and anti-TG antibodies (9). Similarly, in a study by Negro et al., the authors have concluded that anti-TPO antibody levels were higher in patients with severe preeclampsia while anti-TG antibody levels were lower than those of patients with mild preeclampsia (10). Meccacci et al. have also stated that the anti-TPO antibody levels in women with preeclampsia were significantly higher than those of healthy pregnant women (11). The results of our study were also in line with these two studies with regards to anti-TPO and anti-TG levels. We have, on the other hand, found that there was a significant relationship only between patients with mild preeclampsia and thyroid autoantibody levels when we classified the patients as those with severe or mild preeclampsia as different from the mentioned study. We believe that this result is related to the rather limited number of patients with severe preeclampsia. In a study by Männistö et al. that evaluated the relationship between maternal thyroid function disorders and autoantibody positivity and pregnancy complications, the authors proved the predictive values of these parameters neither for preeclampsia nor maternal mortality (8). While the results of our study indicated a relationship between autoantibody titers and preeclampsia, there was no relationship between antibody positivity and preeclampsia development when the patients were grouped in terms of autoantibody positivity and negativity. There were only a limited number of patients with euthyroid autoantibody positivity. However, although Männistö et al. had conducted their study with a sufficient number of antibody positive patients, they were not able to establish a relationship between preeclampsia development and antibody positivity either.

Pregnancy is related to significant and mostly reversible alterations in thyroid functions. While a decrease is observed in TSH levels in the first half of pregnancy, an increase within normal bounds is seen in the second half (12).

In spite of the fact that physiological changes in thyroid functions during pregnancy are well-established, there is again a limited number of studies on changes in thyroid functions in preeclamptic pregnant women and the fetal effects of these (13). While no significant difference was found in the comparisons among the three groups pertaining especially to TSH levels within the framework of our study, fT3 and fT4 levels were both found to be higher in both preeclamptic and healthy pregnant women than non-pregnant women. Qublan et al. have found that there was no significant difference between healthy and preeclamptic women with regards to free T3 and free T4 in their recent study conducted with 27 patients with severe preeclampsia (14). In their comparative study conducted with 82 preeclamptic pregnant women and 82 healthy pregnant women in their latest trimester, Kumar et al. have shown a correlation between preeclampsia development and elevated TSH and T4 and low T3 levels (15). Furthermore, in a similar study by Lao et al., the authors have reported that preeclamptic pregnant women had high TSH and low fT3 and fT4 concentrations when they compared 24 normotensive pregnant women with 39 pregnant women with proteinuria-preeclampsia (16). Volvodik et al. have also found similar results in their study conducted with 15 euthyroid patients with preeclampsia that developed in their third trimester compared to 20 healthy pregnant women (17). In a study by Zhou et al., the authors have reported lower thyroid hormone levels and higher TSH levels in both groups with mild and severe preeclampsia but all hormone concentrations were at a comparable level in both mild and severe preeclampsia groups (18). There is again only a limited number of studies aiming to explain the pathophysiology between thyroid function tests and preeclampsia. Basebug et al. have ascertained a significant relationship between maternal endothelin levels blamed in the pathogenesis of preeclampsia/eclampsia and all thyroid function tests (19). In a study by Levine et al., the authors also argued that the correlation between thyroid function tests and autoantibodies and gf-like tyrosine kinase-1 accounted for the pathophysiology of preeclampsia (20).

Furthermore, the results of our study revealed no significant correlation among hypertension, which proves to be a diagnostic criterion for preeclampsia, thyroid hormones

and thyroid antibodies as well. In accordance with the results of our study, Raoofi et al. were not able to ascertain a significant difference among systolic and diastolic blood pressure levels and TSH and fT4 concentrations in their study conducted with 100 pregnant patients with preeclampsia and 101 normal pregnant women (21). No previous study that was conducted on the relationship between hypertension and thyroid autoantibodies could also be found in literature.

The renal function test results of preeclamptic patients can both be normal and abnormal. Previous studies have shown that while creatinine clearance and serum creatinine rates were generally within normal limits in mild preeclampsia, a pronounced disorder was seen in patients with severe preeclampsia (22,23). Makuyana et al. reported in their study that the BUN and creatinine values were significantly higher in the preeclamptic cases than the normotensive group when evaluated with regards to renal functions. Similarly, Taşın et al. stated that the BUN and creatinine levels were significantly higher in cases with severe preeclampsia than those of the control and mild preeclampsia groups (24). In line with literature, the results of our study also demonstrated that the urea and creatinine levels were significantly higher in preeclampsia patients than the control group. This disorder, however, was not related to the thyroid hormones and autoantibodies.

Preeclampsia, specifically severe preeclampsia, is related to hemolysis, elevated liver enzymes, and low platelet count which are referred to as the HELLP syndrome (25). We, too, have investigated the correlation between thyroid autoantibodies and thyroid functions as a sub-group of our study with platelet values. In spite of the fact that even normally progressing pregnancy poses a risk for low platelet levels, studies in literature, which have investigated the changes seen in platelet parameters during pregnancy in pregnant and non-pregnant women, have reported different results (26,27). Especially some studies have reported that the platelet count in the third trimester of pregnancy was lower than that of normal women (28).

Akingbola et al. have stated in their study that the platelet counts in normal pregnant women were similar in the first and second trimesters but that they decreased in the third trimester (29). The results of our study revealed that the platelet counts of both healthy pregnant women and patients with preeclampsia were lower than those of non-pregnant women. There was, however, no difference between the platelet counts of healthy and preeclamptic pregnant women. The results of previous studies which have investigated the effects of preeclampsia on platelet counts were inconsistent as well (30, 31). Neiger et al. have stated that the immediate prenatal platelet count was lower in the preeclamptic group than the normal pregnant women and that there was no difference between mild and severe preeclampsia (32). As opposed to this, many studies have reported that platelet count in preeclamptic women were different than that of normal pregnant women in line with our results. On the other hand, the results of our study did not reveal any correlation neither between low platelet count and thyroid hormones nor between the former and the antibody titer in preeclamptic patients. Moreover, our literature review did not disclose any similar study that investigated the relationship between platelet counts and thyroid hormones and autoantibodies.

The results of liver function tests are generally within normal limits in most of the patients, while they are so in 20-30% of the patients with mild preeclampsia. Makuyana et al. found in their study that there was no difference between normotensive and preeclampsia cases with regards to ALT levels, while the authors ascertained that AST levels were significantly higher in preeclampsia cases (24). In a study by Taşın et al., ALT and AST levels were found to be significantly higher in the severe preeclampsia cases while no significant differences were determined between the control group and mild preeclampsia cases (33). In our study, ALT levels were found to be higher in the mild preeclampsia group as revealed by the comparisons conducted between the mild preeclampsia group and the pregnant and control groups. Moreover, AST levels were found to be significantly higher in the severe preeclampsia group in comparisons carried out among the control group and the mild preeclampsia group, severe preeclampsia group, and the healthy pregnant group. The results of our study regarding liver function test comparisons between preeclamptic patients and normal pregnant women were concordant with literature. When the ALT levels were evaluated on its own merits, however, it was determined that they were higher in the mild preeclampsia group while AST levels were higher in the severe preeclampsia group. On the other hand, we were not able to pinpoint a correlation among AST and ALT levels, and thyroid hormones and thyroid autoantibodies, as was the case with platelet count.

CONCLUSION

Pregnancy is related to significant and reversible alterations in thyroid functions. The physiological changes in thyroid functions during pregnancy are well-established. Available information on the relationship between thyroid function alterations and thyroid autoantibody positivity with the severity of preeclampsia, however, still proves to be limited.

The results of our study suggest that especially low levels of free T3 and free T4 may play a role in preeclampsia development. We were, however, not able to establish a relationship between preeclampsia development and thyroid autoantibodies that might be significant. Nevertheless, we believe that although thyroid autoantibodies would play a role in the development of this disease concerning significantly higher anti-TPO in preeclamptic pregnant women than healthy pregnant women, this role would be played by anti-TPO.

Competing interests: The authors declare that they have no competing interest.

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