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Correlation of Autoimmune Markers with Clinical Features in Newly Diagnosed Hypothyroid Patients in Bangladesh

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Abstract

Background: Hypothyroidism is a widespread endocrinological disorder that affects millions of people worldwide. The thyroid gland fails to produce sufficient amounts of thyroid hormones, T4 and T3. Hormonal deficiency causes disturbance of metabolism in the organism and affects multiple organ systems.

Objective: In this study, the objective was to establish a correlation between the demographic, clinical, and serological factors associated with hypothyroidism among patients with special emphasis on their menstrual problems, obstetric history, and thyroid autoimmunity.

Methods: This was a cross-sectional study conducted with 154 patients. The data collection period was from January 2, 2015 to December 31, 2015. Statistical tests, such as Spearman's correlation and multiple regression, were used to establish correlations.

Results: Amenorrhoea was found in 22.7% of patients, while oligomenorrhoea was found in 11.7% of them. No problems during pregnancy were recorded in 50% of patients, while 16.2% suffered from spontaneous abortion, which was the most frequent complication among all other mentioned issues. There were no relations between anti-TPO and anti-Tg antibodies and TSH/FT4 concentrations; nonetheless, a significant association between these antibodies and grade 1 goitre (OR 11.7, $p<0.001$) was found. Weight gain was observed in 73.4% of antibody-positive patients ($p<0.043$).

Conclusion: Hypothyroidism is accompanied by considerable menstrual and obstetric problems, while thyroid autoimmunity is related to morphological changes in the gland, including goitre and weight gain. The absence of any relation between antibodies and TSH/FT4 levels indicates complicated immune mechanisms.

Keywords: Hypothyroidism, Menstrual irregularities, Obstetrical history, Anti-TPO antibodies.

INTRODUCTION

Hypothyroidism is a widespread endocrinological disorder that affects millions of people worldwide. The

thyroid gland fails to produce sufficient amounts of thyroid hormones, T4 and T3. Hormonal deficiency causes disturbance of metabolism in the organism and affects multiple organ systems [1]. Thus, hypothyroidism may affect the cardiovascular, gastrointestinal, musculoskeletal, and neuropsychological systems, which makes the disease very significant from a medical point of view [2]. The prevalence rate of overt hypothyroidism in the general population is estimated at about 5%, and another 5% suffer from subclinical hypothyroidism in iodine-sufficient regions [3].

Autoimmune thyroiditis, especially Hashimoto's thyroiditis, is the most common cause of hypothyroidism in areas where there is sufficient amount of iodine available [4]. Hashimoto's thyroiditis is an autoimmune disease characterized by the formation of autoantibodies, including thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), that cause the progressive destruction of thyroid follicular cells [5]. High levels of TPOAb and TgAb are important indicators for the detection of autoimmune thyroiditis and indicate the degree of dysfunction in the thyroid gland [6]. These autoantibodies inhibit the production of hormones by damaging the enzymes and proteins required in the production of hormones.

The manifestations of hypothyroidism may vary from general, unspecific signs to severe complications that may become deadly. Some of the common manifestations include fatigue, weight gain, intolerance to cold, constipation, dry skin, and hair loss [7]. Bradycardia, myxedema, infertility, and cognitive impairment are some of the more severe manifestations. The chronic irritation of the thyroid gland often results in the development of goiter, particularly when there is a lack of iodine intake in the diet. However, not all patients experience classical manifestations of the condition [8].

The role of autoantibody markers like TPOAb and TgAb in the development of hypothyroidism remains the key issue in scientific studies. The increased level of these antibodies is a good marker of autoimmune thyroiditis and the level of its severity [9]. Scientific literature shows the connection between increased TPOAb and TgAb with the severity of thyroid dysfunction and an increase in the number of symptoms [10]. In spite of all the information about these connections, the difference in the levels of markers and symptoms proves the need for further research in this direction. Understanding these connections will help obtain some valuable information concerning the disease pathology and its treatment [11].

The country provides a unique setting for hypothyroidism research owing to its distinct socio-demographic and nutrition profile. The problem of iodine deficiency has been solved through the introduction of iodized salt programs. However, the existing regional differences in iodine intake, as well as genetic predispositions and healthcare-seeking behaviors, continue to influence the prevalence rate and symptoms of hypothyroidism[12]. The Bangabandhu Sheikh Mujib Medical University (BSMMU) is an outstanding teaching and referral hospital that can provide a perfect opportunity for hypothyroidism research among Bangladeshi people. It provides access to patients with different socioeconomic and geographic characteristics, thus allowing conducting a comprehensive investigation of autoimmune thyroid diseases. The ain of this study was to establish correlations among the demographic, clinical, and serological characteristics of hypothyroid patients, emphasising menstrual health, obstetric history, and thyroid autoimmunity.

Methods

Study Design: The study design for this project was cross-sectional observational to investigate the effect of anti-thyroid antibodies on thyroid hormone levels in new cases of hypothyroidism. Information was collected between January 2, 2015, and December 31, 2015.

Location of this Study: This research was conducted in the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. BSMMU is a tertiary care center where many types of patients are seen; thus, this will be an excellent place to conduct research on thyroid diseases among diverse patients

Inclusion Criteria:

- Adult individuals aged 18 years or above are diagnosed with hypothyroidism recently. It means they have high TSH concentration with low free T4 level.
- The individuals have not received any previous treatment related to the dysfunction of the thyroid gland.
- The patients are willing to give an informed consent and adhere to the conditions of the research.

Exclusion Criteria:

- Patients who suffer from secondary or central hypothyroidism such as the problem with pituitary gland or hypothalamus.
- Those who are diagnosed with non-thyroidal illness syndrome or other systemic diseases that influence the functioning of thyroid.
- Females who are pregnant or nursing.
- Those who have been operated on thyroids, used radioactive iodine or levothyroxine.
- Individuals who had autoimmune disorders, such as systemic lupus erythematosus or rheumatoid arthritis.

Sample Size: The computation for the sample size ensured enough statistical power to determine any correlations between TPOAb/TgAb values and the thyroid function. A total of 154 participants were included based on the estimated effect size of 0.3, at a confidence level of 95% and power of 80%.

Sample size calculation: The following formula is used for calculating the sample size of the study population:

n = z2pq / d2

p = Proportion or percentage of prevalence (based on the increasing prevalence noted in some studies) = 30-40% (11).

q = (1 – p) = 100 – 40 = 60%

Value of the standard normal distribution (z distribution) at a particular level of significance or confidence interval (1.96 at 95% confidence level, which is always constant) is z.

d = margin of error over the rate of occurrence (20% of 40)

Therefore, from the above formula,

n = [(1.96)2 x 40 x 60] / [(20 x 40)/100]2

= (3.8416 x 2400) / [(20 x 40)/100]2

= 9219.84 / 64

= 144.06 (145)

The study has a sample size of 145.

Outcome Variables

Primary Outcome Variables

The primary outcome variables of this study were the thyroid functional markers: The serum levels of TSH (thyroid stimulating hormone), the serum levels of free T4and the serum levels of free T3. These

outcome variables were employed to assess the functional status of the thyroid gland among recently detected cases of hypothyroidism.

Secondary Outcome Variables

The secondary outcome variables were: The level of antibodies to thyroid:, thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb),. The severity of symptoms of hypothyroidism (on the basis of validated symptom score questionaire), and the presence of goitre/thyroid enlargement on physical examination

Exposure Variables: The levels of TPOAb and TgAb were regarded as exposure variables in order to determine their relationship with thyroid function parameters.

Variables: The variables considered in the study were as follows: Age, Sex, Body Mass Index (BMI), Iodine consumption in diet, Smoking, and Socioeconomic & Healthcare Access Factors.

Outcome: The outcome considered for the analysis were the following: Thyroid Function Parameters (TSH, free T4, free T3), which were continuous in nature. Antibody levels (TPOAb, TgAb) were examined as both continuous and categorical (positive/negative)**.**

Data Collection Procedure: Detailed medical history to document symptoms, duration of illness and family history of any autoimmune diseases and/or thyroid abnormalities. Clinical examination to examine thyroid gland by palpation for the presence of goiter or thyroid nodules. The chemiluminescent immunoassay (CLIA) technique was used to test serum levels of TSH, FT4 and FT3 in order to assess the thyroid function.

Autoantibody Levels: Thyroglobulin autoantibodies (TgAb) and thyroid peroxidase autoantibodies (TPOAb) were tested using enzyme-linked immunosorbent assay (ELISA). Sociodemographic and Lifestyle Factors: Standardized questionnaires will be used to obtain information on age, gender, BMI, iodine intake via diet, smoking habits, and access to health care facilities.

Scoring the Severity of Symptoms: Subjects will be asked to score their symptoms of hypothyroidism through standardized questionnaire**.**

Analysis of Data: Descriptive analysis for mean, median, and frequency distributions to describe the patient characteristics, clinical features, and biochemical markers. Correlation analysis for to evaluate the relationship between levels of TPOAb/TgAb and thyroid function parameters such as TSH, free T4, and free T3; either Pearson or Spearman correlation coefficients will be utilized. Multivariate linear regression models will determine the effects of TPOAb/TgAb levels on thyroid function independently from confounders like age, gender, and BMI.

Ethical Considerations: The current study received approval from the IRB of Bangabandhu Sheikh Mujib Medical University (NO. BSMMU/2015/0004), Shahbag, Dhaka, Bangladesh at the 257th IRB session dated 21st June 2015. Informed consent was taken from all the subjects prior to including them in the present study. The experiments performed on human subjects were conducted according to the guidelines recommended by the Institutional Review Board as well as Declaration of Helsinki, 1964 and its subsequent amendments.

Results

As seen in the study graph 1, participants' mean age was 36.07 years (SD ± 11.00). Of the total participants involved, 29.9% were males, while 70.1% were females. 9.1% of the participants reported that there was a history of thyroid disease in their families. This indicates that inherited thyroid disorders are not very

common among this study group of participants. Based on residence, 27.3% of the participants resided in urban areas, while 72.7% resided in rural areas.

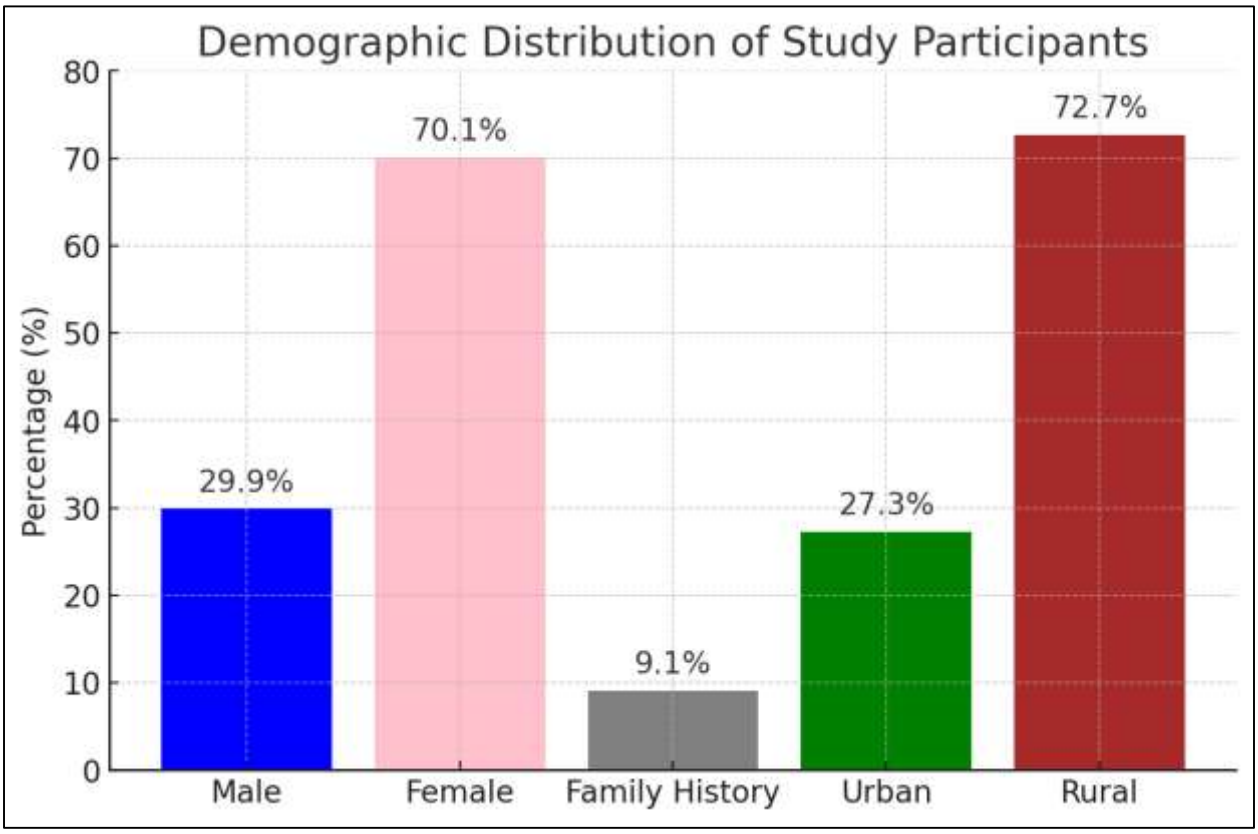

Figure 1: Characteristics of the newly detected adult hypothyroid patients

Figure 2 shows that there were many participants who suffered from amenorrhoea and oligomenorrhea, and there was a smaller number of participants who had other menstrual irregularities. Overall, it is clear from the outcomes that there were various cases of menstrual health among participants. There was a substantial number of participants (46 or 29.9%) who claimed that they did not suffer from any menstrual problems. There were 35 participants (22.7%) who had amenorrhoea, meaning that there was no menstruation. There were 18 participants (11.7%) who had oligomenorrhoea, meaning that their menstrual cycles were not regular. There were 16 participants (10.4%) who had menstrual irregularities. There were 15 participants (9.7%) who suffered from menorrhagia, which means heavy menstrual bleeding.

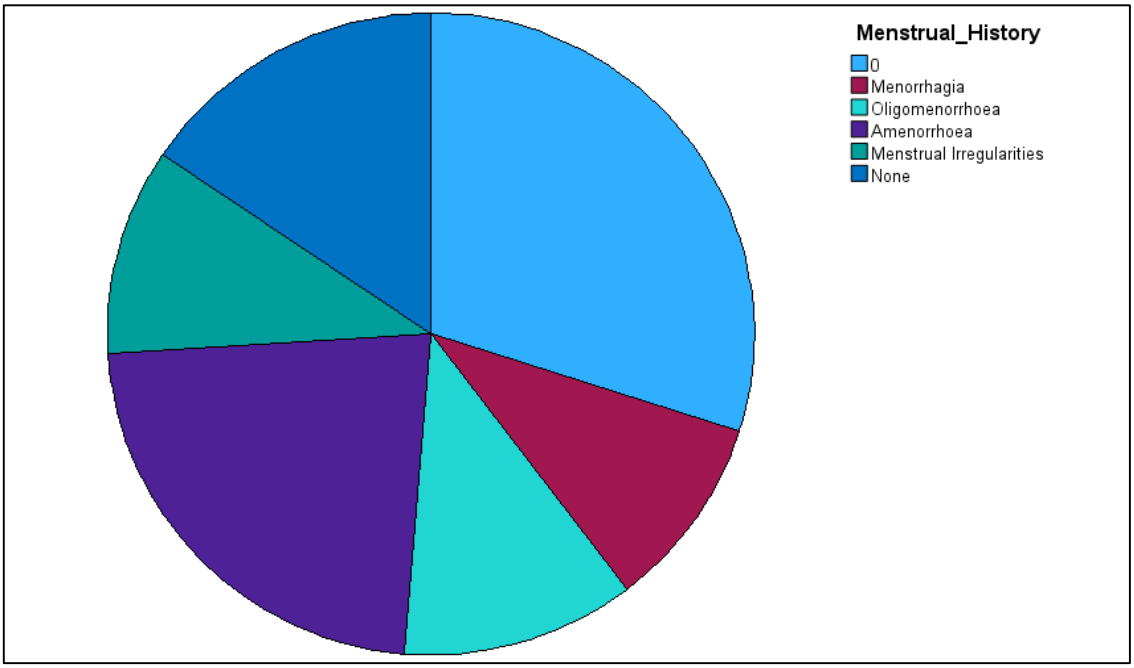

Figure2: Menstrual history of the subjects

According to the findings presented in Figure 3, this research proposes that half of the subjects did not have any negative obstetric experiences, while the remaining half struggled with problems and the most frequent problem was spontaneous abortion. In total, the frequency of adverse obstetric history among the total number of 154 subjects is presented below: No history of adverse obstetric events – 29.9% (46 subjects). Spontaneous abortion – 16.2%. History of IUFD – 3.9%.

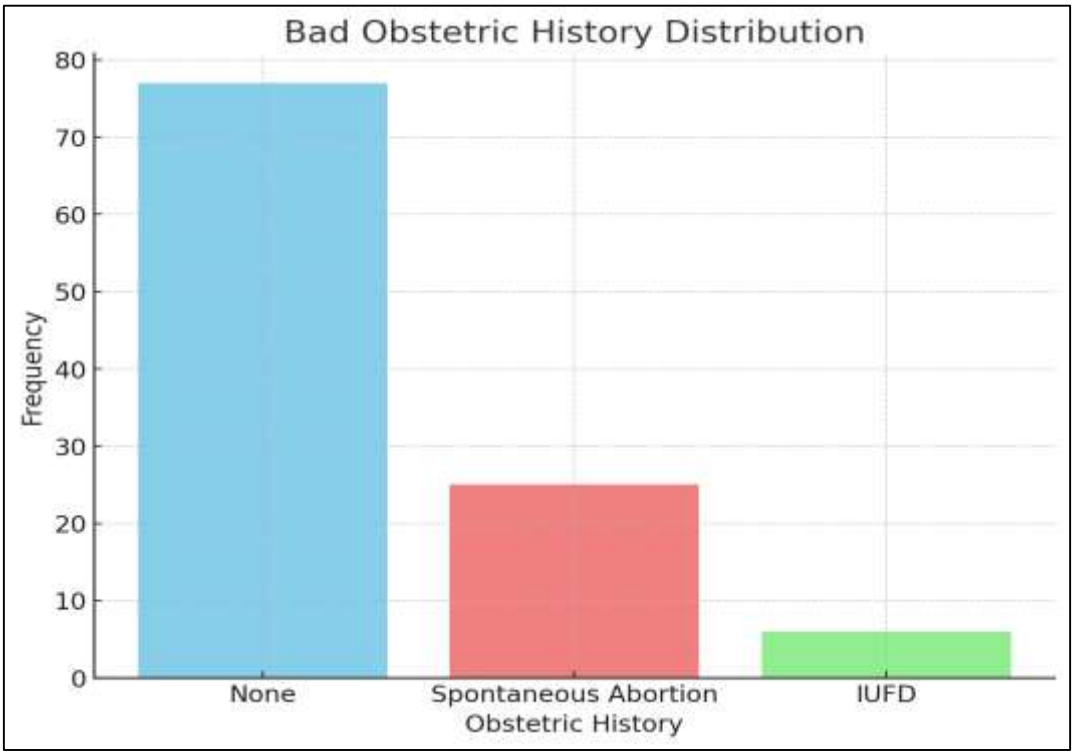

Figure3: Bad obstetric history distribution of the subjects

A large number of people had amenorrhea and oligomenorrhea, whereas some had other menstrual disorders. It has been found that different menstrual health experiences were encountered by the participants.

In total, a substantial number of the participants (46 or 29.9%) did not experience any menstrual disorder. In total, 35 participants (22.7%) had amenorrhea, which is described as absence of menstruation. 18 participants (11.7%) experienced oligomenorrhea, which is described as infrequent menstrual cycles. 16 participants (10.4%) had menstrual disorders, which might be attributed to variations in menstrual cycle or flow. Also, menorrhagia was experienced by 15 participants (9.7%). Lastly, 24 participants (15.6%) did not have any menstrual problem (Figure 4)

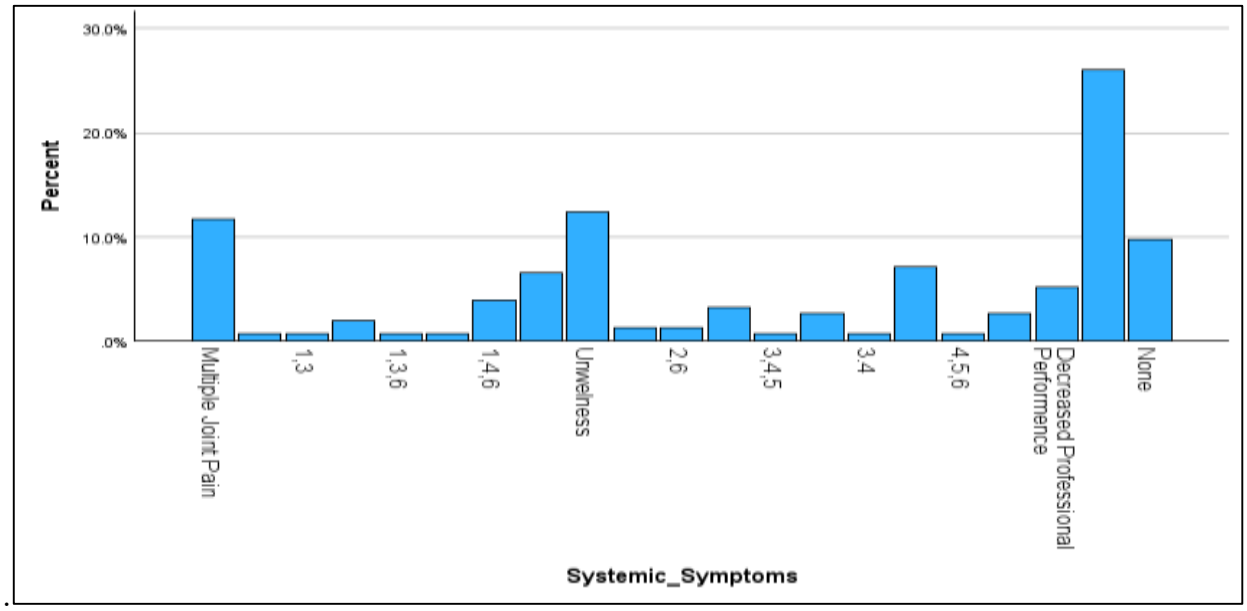

Figure4: Systematic symptoms of the subjects

The presenting complaints of adult hypothyroidism patients are shown in table 1 below. Seventy-three percent of the patients reported complaints of weight gain, and there was an increased prevalence of anti-thyroid antibodies ($p<0.043$). Despite all the other symptoms being prevalent in patients with anti-thyroid antibodies, no statistically significant difference was noted. Table 2 below illustrates the status of thyroid function of the newly diagnosed cases of hypothyroidism. There was no statistically significant effect of anti-thyroid antibodies on FT4 and TSH levels.

Table 1: Thyroid function and autoimmune status of the newly detected hypothyroid patients

Laboratory findings	Total	Anti body		P value
		Positive (n=137) Mean ± SD	Negative (n=17) Mean ± SD	
FT4 (ng/dl)	0.46 ± 0.18	0.46 ± 0.18	0.48 ± 0.17	0.666
TSH(ulU/ml)	86.61 ± 49.93	86.81 ± 49.19	84.95 ± 57.19	0.885

Student's T-test was done to measure the level of significance

The spearman correlation of serum Anti TPO and anti Tg titer with FT4 or TSH were not significantly correlated ($p > 0.05$) except for a negative relationship between anti-Tg and FT4 that reached statistical significance level ($r = -0.158$, $p < 0.05$). The presence of a positive correlation between anti TPO and anti-Tg titer was reported ($r = 0.198$, $p < 0.014$).

Table 2: Correlation of Anti-TPO and Anti-Tg with FT4 and TSH

	r value	p value
Anti-TPO titer vs. FT4	-0.068	0.402
Anti-TPO titer vs. TSH	0.077	0.344
Anti-Tg titer vs. FT4	-0.158	0.050
Anti-Tg titer vs. TSH	-0.037	0.650
Combined Anti-TPO and Anti-Tg vs FT4	0.041	0.615
Combined Anti-TPO and Anti-Tg vs TSH	-0.014	0.862
Anti-TPO titer vs. anti-Tg	0.198	0.014

(Spearman correlation test was done to measure the level of significance)

Table 3 demonstrates multiple regression analysis using anti-TPO and anti-Tg antibody as an independent variable. In this case, grade 1 goitre was significantly linked to positive anti-thyroid antibody ($p < 0.001$, OR 11.766; 95% CI 2.992 – 46.266). In the case of grade 1 goitre, the probability of getting positive thyroid antibody is 11.7 fold.

Table 3: Multiple regression analysis with anti-TPO and anti-Tg antibody as dependent variable

	B	S.E.	Wald	p-value	OR	95% CI of OR	
						Lower	Upper
Age	-0.005	0.025	0.049	0.825	0.995	0.947	1.044
Sex (male)	0.239	0.594	0.161	0.688	1.270	0.396	4.071
Residence (rural)	-0.193	0.671	0.082	0.774	1.212	0.325	4.516
Goiter (Grade 1)	2.465	0.699	12.454	0.001	11.766	2.992	46.266
Goiter Grade 2)	1.148	0.721	2.538	0.111	3.153	0.768	12.952
FT4	1.265	2.073	0.373	0.542	3.544	0.061	206.09
TSH	-0.001	0.008	0.008	0.931	0.999	0.984	1.015

Discussion

This current study investigated the clinical, demographic, and serological characteristics of hypothyroid patients, paying special attention to menstrual abnormalities, obstetric history, and thyroid autoimmunity. Several important outcomes of this research deserve mentioning; some of them correspond to and some are different from those of other studies conducted on this topic [13]. On average, the age of people involved in the research was 36.07 years old; most of them were females who lived in rural areas. This is also confirmed by the other literature that states that thyroid diseases are more common among women especially at reproductive age [14]. The small number of patients having a family history of thyroid diseases contradicts the other studies where heredity played an important role.

Many participants had menstrual disturbances, and amenorrhoea and oligomenorrhoea were the two most prevalent disorders among them. This finding is supported by previous studies that established the association between hypothyroidism and menstrual disturbances arising from impaired regulation of the hypothalamus-pituitary-ovary axis [15,16]. Nevertheless, the substantial number of women without any menstrual disturbances points out that thyroid dysfunction does not always affect menstrual cycles.

Fifty percent of the subjects did not experience any obstetrical complications, and spontaneous abortion turned out to be the most common one. This confirms the results of [17,18] who found that autoimmune thyroid disease is associated with miscarriage independent of thyroid status. Since there was no association between the presence of antithyroid antibodies and the serum levels of TSH/FT4, it could be supposed that the development of pregnancy loss might be linked to immune disorder, not hypothyroidism.

The presence of anti-TPO and anti-Tg antibodies was found to have no correlation with TSH and FT4 serum concentrations, unlike a number of other studies that state the connection between antibody titers and severity of the disease [17]. However, there is a high correlation between Grade 1 goiter and positive tests for antibodies, which reflects the theory that thyroid autoimmunity leads to structural changes in the gland [21]. The most common complaint was weight gain, which correlated significantly with the results of the study. Similar findings have been previously observed, although the exact mechanism of how this happens is unknown [22,23].

Limitations and Further Studies: Since the current research uses a cross-sectional design, the ability to make cause-and-effect relationships is limited. In addition, since there is no long-term observation period, it is difficult to assess the development of diseases. Multicentre and large-scale studies might be used for verifying these results among different populations.

Conclusion:

This study reveals hypothyroidism, disorders of menstruation, and complications during pregnancies. Autoimmunity of the thyroid gland plays a crucial role in the development of goitre. Some findings confirm those of the earlier studies, but the absence of the relationship between antibodies and hormones indicates more complicated mechanisms. Thus, future studies must focus on the molecular mechanisms responsible for such a relationship.

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