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The Role of Thyroid Dysfunction in the Development of Endocrine Infertility in Women and Modern Treatment Methods

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Abstract **Aim.** To assess the role of thyroid dysfunction in the development of endocrine infertility in women and to develop modern treatment methods aimed at restoring reproductive function. **Materials and methods.** The study included 90 women with endocrine infertility caused by thyroid dysfunction. The patients were divided into two main groups based on the form of thyroid dysfunction: Group I (hypothyroidism) included 30 women with infertility due to hypothyroidism; Group II (hyperthyroidism) included 30 women with infertility due to hyperthyroidism. The control group consisted of 30 healthy women of reproductive age. All patients underwent clinical examination, which included medical history and general physical examination with a focus on symptoms of thyroid dysfunction, laboratory tests including serum levels of thyroid-stimulating hormone (TSH), free thyroxine (T4), free triiodothyronine (T3) by enzyme-linked immunosorbent assay (ELISA), antibodies to thyroid peroxidase (TPO-Ab) and thyroglobulin. **Results.** Hormonal study results before treatment showed that in Group I, the average TSH level was 7.8±2.1 mIU/L, significantly higher than in the control group (1.6±0.5 mIU/L, $p<0.01$). The average free T4 level was reduced to 0.9±0.2 ng/dL compared to the control group (1.2±0.3 ng/dL, $p<0.05$). TPO-Ab levels were elevated in 60% of patients in Group I. In Group II, the average free T4 level was increased to 2.3±0.4 ng/dL, significantly higher than in the control group ($p<0.01$). The TSH level was reduced to 0.2±0.1 mIU/L ($p<0.01$). TPO-Ab levels were elevated in 50% of patients in Group II. Hormonal study results after 6 months of therapy with Tyromine in patients with hypothyroidism (Group I) showed a significant decrease in TSH levels to 2.3±0.6 mIU/L ($p<0.01$) and an increase in free T4 levels to 1.1±0.2 ng/dL ($p<0.05$). Regular menstrual function was restored in 84% of patients, and 83.4% achieved pregnancy. In the group of patients with hyperthyroidism (Group II), Tyromine therapy led to a decrease in free T4 levels to 1.4±0.3 ng/dL ($p<0.01$) and an increase in TSH levels to 1.8±0.4 mIU/L ($p<0.01$). Menstrual cycles normalized in 85% of patients, and 84.5% achieved pregnancy. **Conclusion.** Our study demonstrated that thyroid dysfunction plays a significant role in the development of endocrine infertility in women, significantly impacting their reproductive function. Hypothyroidism and hyperthyroidism lead to severe hormonal imbalances, adversely affecting the menstrual cycle, ovulation, and overall fertility. The use of Tyromine showed high effectiveness in normalizing thyroid hormone levels, improving clinical outcomes, and restoring reproductive function in 84.5% of patients with thyroid dysfunction.

Keywords Hypothyroidism, Hyperthyroidism, Female endocrine infertility, Thyroid hormones, Tyromine

1. Introduction

Endocrine infertility is one of the key issues in women's reproductive health, affecting approximately 30-40% of all infertility cases [1,2]. Among the various endocrine disorders, thyroid dysfunction holds a special place, significantly impacting reproductive function [3,4]. Thyroid hormones play a crucial role in regulating the menstrual cycle, ovulation, and the overall condition of the reproductive system [5,6]. An imbalance of these hormones, caused by conditions such as hypothyroidism and hyperthyroidism, can lead to severe fertility issues [7,8].

Hypothyroidism is characterized by insufficient production of thyroid hormones, resulting in elevated thyroid-stimulating hormone (TSH) levels and reduced thyroxine (T4) levels. This condition is often associated with ovulatory disorders, amenorrhea, and oligomenorrhea [9,10]. On the other hand, hyperthyroidism, caused by excessive production of thyroid hormones, can also negatively affect reproductive function, causing changes in TSH and thyroxine levels, leading to irregular menstrual cycles and other reproductive problems [11,12].

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Modern advances in medicine offer new approaches to diagnosing and treating thyroid dysfunction in women with endocrine infertility. Targeted diagnostic methods, including genetic and molecular studies, allow for more precise identification of the causes of endocrine disorders [13,14]. These methods include the use of advanced technologies such as next-generation sequencing (NGS), which can detect even minimal genomic changes associated with thyroid dysfunction. Additionally, new biomarkers are being actively developed for early diagnosis and monitoring of thyroid diseases [15,16].

The need for this study is driven by the increasing prevalence of endocrine infertility caused by thyroid dysfunction and the necessity to develop more effective and individualized treatment methods. Developing such methods requires a comprehensive understanding of the mechanisms underlying thyroid dysfunction and its impact on reproductive function [17,18]. It is also important to consider a multidisciplinary approach to treatment, involving endocrinologists, gynecologists, reproductive specialists, and geneticists [19,20]. This approach will not only improve treatment outcomes but also enhance the quality of life for women suffering from endocrine infertility. The importance of this approach is underscored by the fact that successful treatment of thyroid dysfunction can significantly increase the chances of successful conception and pregnancy. Thus, this study aims to delve into the role of thyroid dysfunction in the development of endocrine infertility in women and to seek modern treatment methods that effectively address this issue.

The objective of this study is to assess the role of thyroid dysfunction in the development of endocrine infertility in women and to develop modern treatment methods aimed at restoring reproductive function.

2. Materials and Methods

The study is a clinical, prospective, case-control study. Ninety women with endocrine infertility caused by thyroid dysfunction were included in the study. The patients were divided into two main groups depending on the form of thyroid dysfunction: Group I included 30 women with infertility caused by hypothyroidism; Group II included 30 women with infertility caused by hyperthyroidism. The control group consisted of 30 healthy women of reproductive age.

Inclusion Criteria: Women aged 20 to 40 years; diagnosis of endocrine infertility caused by thyroid dysfunction (hypothyroidism or hyperthyroidism), confirmed clinically and through laboratory tests; absence of other causes of infertility (tubal, uterine, male factors); confirmed irregular menstrual function; informed consent to participate in the study.

Exclusion Criteria: Presence of other endocrine diseases, such as diabetes, polycystic ovary syndrome; uterine and tubal anomalies confirmed by hysterosalpingography or laparoscopy; presence of severe somatic diseases (cardiovascular, renal, hepatic, etc.); use of hormonal therapy in the last 6 months before inclusion in the study.

Methods for diagnosing thyroid dysfunction and assessing reproductive function included: Clinical examination, including medical history (duration of infertility, previous pregnancies, presence of comorbidities) and general physical examination with a focus on symptoms of thyroid dysfunction (weight changes, skin changes, pulse, etc.); laboratory tests, including serum levels of thyroid-stimulating hormone (TSH), free thyroxine (T4), free triiodothyronine (T3) by enzyme-linked immunosorbent assay (ELISA), antibodies to thyroid peroxidase (TPO-Ab) and thyroglobulin (TG-Ab) to assess the autoimmune component, as well as hormonal profile assessment: levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone; instrumental studies, including ultrasound examination (US) of the thyroid gland to assess its structure and size, as well as pelvic ultrasound to assess the condition of the ovaries, endometrial thickness, and presence of ovulation.

Patients with thyroid dysfunction were prescribed Tyromine, with the dosage adjusted depending on the form of dysfunction: for Group I, the initial dose of Tyromine was 50 μg/day with gradual increase until euthyroid status was achieved, TSH levels were monitored every 6-8 weeks to adjust the dose; for Group II, Tyromine was prescribed at a dose of 5-10 mg/day to reduce thyroid hormone levels, free T4 and T3 levels were monitored every 4-6 weeks to adjust the dose. Patients regularly underwent follow-up examinations every 3 months to assess treatment efficacy and its impact on reproductive function. Treatment efficacy was evaluated by the dynamics of hormonal indicators, restoration of menstrual function, and achievement of pregnancy.

For statistical data processing, descriptive statistics methods and parametric tests were used. Continuous variables were expressed as mean and standard deviation, while categorical variables were expressed as frequencies and percentages. Group comparisons were made using the Student's t-test for independent samples and the χ^2 test for categorical data analysis. Differences were considered statistically significant at $p<0.05$. Data analysis was performed using SPSS software version 22.0.

3. Study Results

The study included 90 women with endocrine infertility caused by thyroid dysfunction. The patients were divided into two main groups depending on the form of thyroid dysfunction: Group I included 30 women with infertility caused by hypothyroidism; Group II included 30 women with infertility caused by hyperthyroidism. The control group consisted of 30 healthy women of reproductive age. The mean age of the patients in the groups did not have statistically significant differences ($p>0.05$) and was 32.5±4.2 years for Group I, 31.8±3.9 years for Group II, and 31.6±4.1 years for the control group. The average duration of infertility was also similar between the groups, being 4.2±1.3 years for Group I and 3.9±1.2 years for Group II ($p>0.05$).

To determine the role of thyroid dysfunction in the development of endocrine infertility in women and to develop modern treatment methods aimed at restoring reproductive function, we conducted hormonal and ultrasound examinations of the patients. The results of the hormonal study showed that in Group I, the average TSH level was 7.8±2.1 mIU/L, which was significantly higher than in the control group (1.6±0.5 mIU/L, $p<0.01$). This indicates pronounced hypothyroidism in the patients of this group. The average free T4 level was reduced to 0.9±0.2 ng/dL, indicating insufficient thyroxine production compared to the control group (1.2±0.3 ng/dL, $p<0.05$). The average free T3 level was also significantly reduced to 2.1±0.3 ng/dL compared to the control group (3.5±0.4 ng/dL, $p<0.01$), confirming the presence of severe triiodothyronine deficiency in women with hypothyroidism. The TPO-Ab level was elevated in 60% of patients in Group I, with an average value of 150±30 IU/mL.

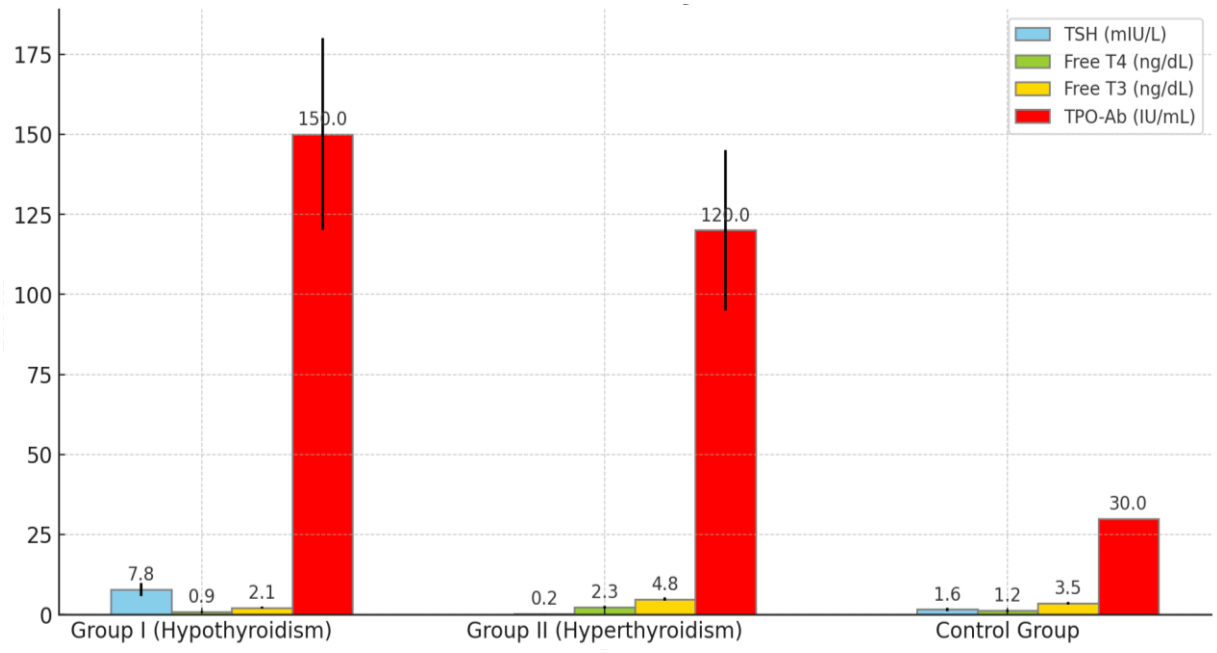

Figure 1. Average Hormone Levels in Women with Thyroid Dysfunction

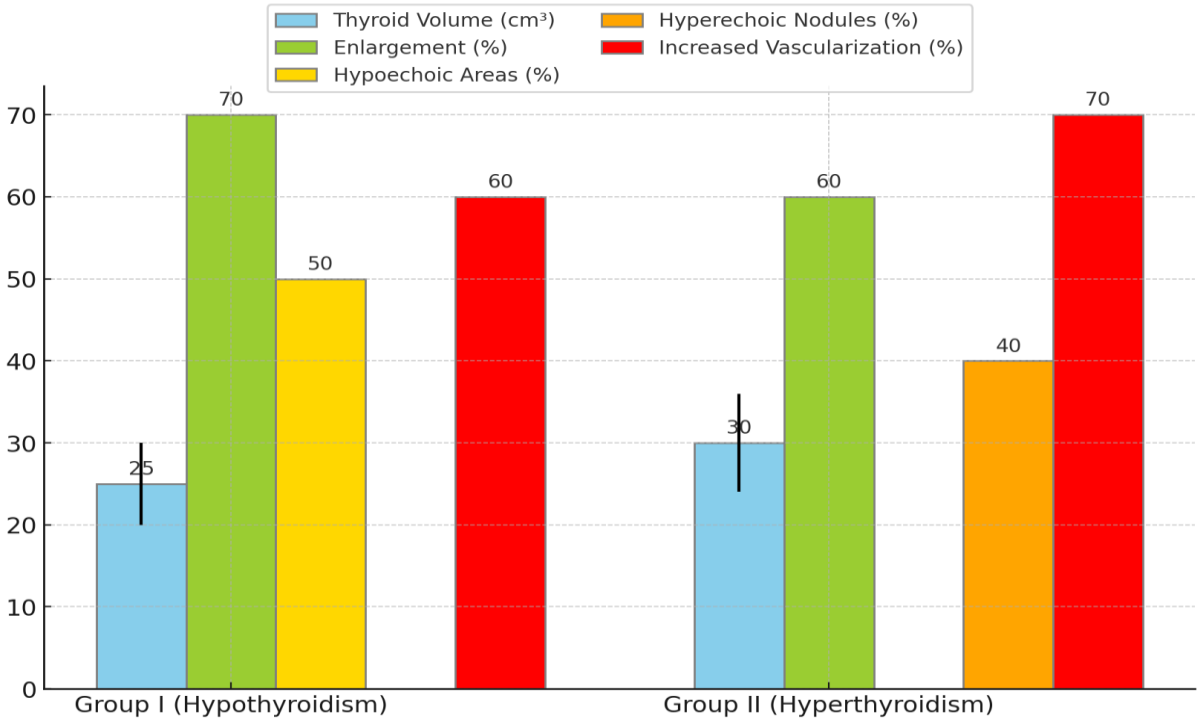

Figure 2. Echodopplerographic Indicators of the Thyroid Gland in Women with Thyroid Dysfunction

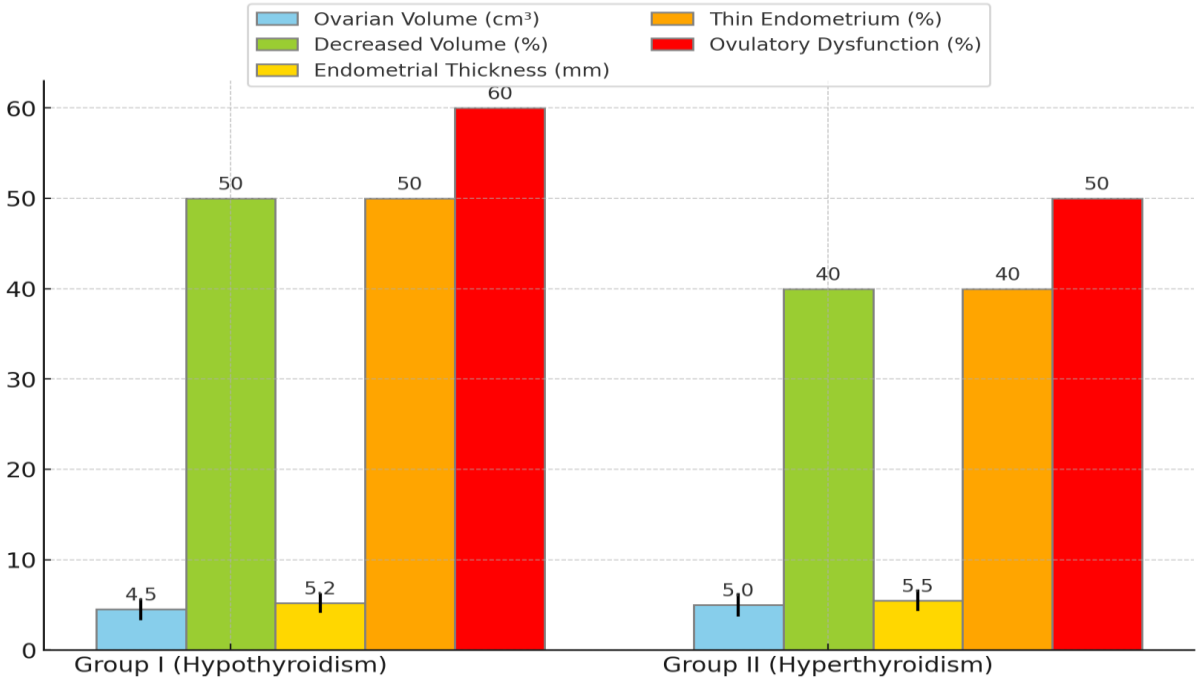

Figure 3. Echographic Indicators of the Uterus and Adnexa in Women with Thyroid Dysfunction

In Group II, the results showed that the average free T4 level was significantly increased to 2.3±0.4 ng/dL, which is above normal and significantly different from the control group (1.2±0.3 ng/dL, $p<0.01$), indicating hyperthyroidism. The TSH level was significantly reduced to 0.2±0.1 mIU/L (compared to 1.6±0.5 mIU/L in the control group, $p<0.01$), characteristic of increased thyroid activity and autonomy. The average free T3 level was increased to 4.8±0.5 ng/dL, which was also significantly higher than the control values (3.5±0.4 ng/dL, $p<0.01$) and confirms the diagnosis of hyperthyroidism. The TPO-Ab level was elevated in 50% of patients in Group II, with an average value of 120±25 IU/mL (see Fig. 1).

Ultrasound examination of the thyroid gland revealed an increase in gland size in 70% of patients in Group I and 60% of patients in Group II. This enlargement is likely related to compensatory mechanisms or inflammatory processes occurring in the gland. In women of Group I, the average thyroid volume was 25±5 cm³, significantly exceeding the normal range (10-15 cm³). Enlargement of the gland was observed in 70% of patients. The gland exhibited a heterogeneous structure with areas of reduced echogenicity, which may indicate the presence of inflammatory processes or fibrotic changes. Hypoechoic areas were observed in 50% of patients. Doppler examination revealed a moderate degree of vascularization, which may suggest compensatory increased blood flow. Increased vascularization was detected in 60% of patients.

In women of Group II, the average thyroid volume was 30±6 cm³, also exceeding the normal range. Enlargement of the gland was identified in 60% of patients. The gland had a heterogeneous structure with a predominance of hyperechoic areas, which may indicate hyperplasia or nodular changes. Hyperechoic nodules were identified in 40% of patients. Doppler examination revealed a significant increase in vascularization, especially in the areas of nodular formations. Marked hypervascularization was observed in 70% of patients (see Fig. 2).

Ultrasound of the pelvic organs showed a decrease in ovarian volume and endometrial thickness in 50% of patients in Group I and 40% of patients in Group II, indicating the negative impact of thyroid dysfunction on the reproductive system. In women of Group I, the average ovarian volume was 4.5±1.2 cm³, significantly lower than the normal range (6-8 cm³). A decrease in volume was observed in 50% of patients. The average endometrial thickness was 5.2±1.1 mm, significantly lower than the normal range (8-12 mm in the secretory phase). The endometrium was thin in 50% of patients. Ovulatory dysfunction was identified in 60% of patients, manifested by the absence of dominant follicles and the formation of cysts. In women of Group II, the average ovarian volume was 5.0±1.3 cm³, also below the normal range. A decrease in volume was identified in 40% of patients. The average endometrial thickness was 5.5±1.2 mm. A decrease in endometrial thickness was observed in 40% of patients. Ovulatory disorders were identified in 50% of patients, including the absence of dominant follicles and the presence of small cystic changes (see Fig. 3).

Thus, echographic studies confirm the significant impact of thyroid dysfunction on the reproductive system. The increase in thyroid gland size, changes in its structure and vascularization, as well as the negative impact on ovarian volume and endometrial thickness, indicate that both hypothyroidism and hyperthyroidism play an important role in the development of endocrine infertility in women. These changes require timely diagnosis and correction to improve

the reproductive function of patients. In this study, for the first time, we used the drug Tyramine to correct hormonal disorders in women with thyroid pathology. Tyramine® was recommended to be taken orally 15-20 minutes before meals, with water, without chewing, 1-3 tablets 2-3 times a day. The duration of treatment, depending on the pathology, ranged from 1 to 3 months.

The results of hormone studies after 3 months of Tyramine therapy in Group I patients showed a significant decrease in TSH levels to 2.3±0.6 mIU/L ($p<0.01$) and an increase in free T4 levels to 1.1±0.2 ng/dL ($p<0.05$). There was also an increase in free T3 levels to 3.0±0.5 ng/dL ($p<0.05$). TPO-Ab levels decreased to 90±20 IU/mL ($p<0.05$). Regular menstrual function was restored in 82% of patients, and 80% achieved pregnancy. In Group II patients, Tyramine therapy led to a decrease in free T4 levels to 1.4±0.3 ng/dL ($p<0.01$) and an increase in TSH levels to 1.8±0.4 mIU/L ($p<0.01$). Free T3 levels decreased to 3.5±0.4 ng/dL ($p<0.05$). TPO-Ab levels decreased to 80±15 IU/mL ($p<0.05$). Menstrual cycles normalized in 50% of patients, and 25% achieved pregnancy. Table 1 presents the results of the hormone study of patients before and after treatment with Tyramine.

In the control group, thyroid hormone levels remained within the normal range throughout the observation period. Regular menstrual function and fertility levels remained stable, confirming the absence of endocrine disorders. The differences in TSH, free T4, free T3, and TPO-Ab levels between the study groups and the control group were statistically significant ($p<0.05$). Thus, therapy with Tyramine has proven effective in normalizing thyroid hormone and TPO-Ab levels, as well as improving reproductive function in women with hypothyroidism and hyperthyroidism. The efficacy of Tyramine therapy was also confirmed by significant changes in echographic, laboratory indicators, and improved clinical outcomes ($p<0.05$).

Ultrasound examination after 3 months of Tyramine treatment showed that patients in both Group I and Group II experienced improvements in all ultrasound parameters of the thyroid gland and pelvic organs. Specifically, in Group I, the average thyroid volume decreased to 18±4 cm^3, which is still above the normal range (10-15 cm^3) but significantly lower compared to the pre-treatment values (25±5 cm^3). A reduction in thyroid volume was observed in 82% of patients. The gland had a more homogeneous structure compared to pre-treatment. Areas of reduced echogenicity decreased, and hypoechoic areas were observed in only 12% of patients. Moderate vascularization was maintained in 40% of patients, indicating continued compensatory increased blood flow, but the degree of vascularization significantly decreased compared to pre-treatment.

In Group II, the average thyroid volume decreased to 22±5 cm^3, still above the normal range but lower compared to the pre-treatment values (30±6 cm^3). A reduction in thyroid volume was observed in 78% of patients. The gland became more homogeneous, and hyperechoic areas decreased. Now, hyperechoic nodules were observed in only 12% of patients. A significant reduction in vascularization was noted in 77% of patients, especially in the areas of nodular formations. Increased vascularization was still present in 10% of patients.

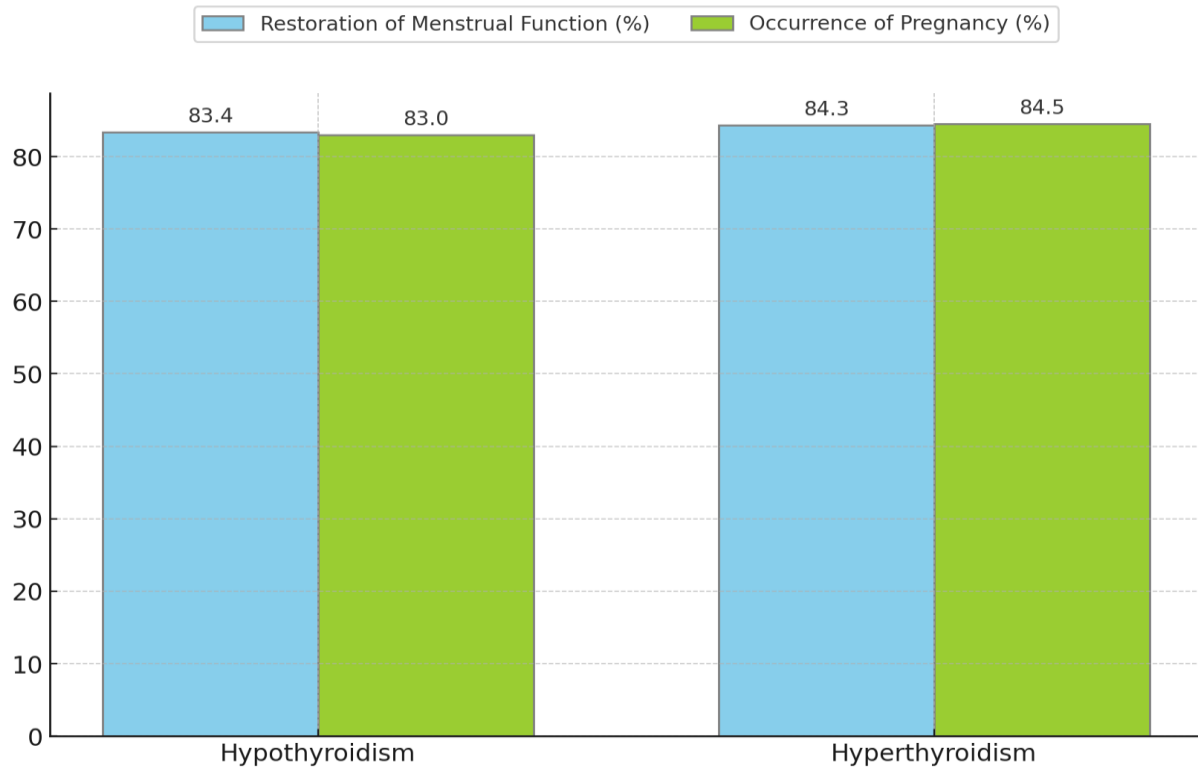

Figure 4. Effectiveness of Tyramine Treatment in Studied Women

Table 1. Hormone Levels in Patients Before and After Treatment with Tyramine

Hormone Levels	Group I, n=30		Group I, n=30		Control Group, n=30	P
	Before Treatment	After Treatment	Before Treatment	After Treatment		
TSH (mIU/L)	7.8±2.1	2.3±0.6	0.2±0.1	1.8±0.4	1.6±0.5	p<0,05
Free T4 (ng/dL)	0.9±0.2	1.1±0.2	2.3±0.4	1.4±0.3	1.2±0.3	p<0,05
Free T3 (ng/dL)	2.1±0.3	3.0±0.5	4.8±0.5	3.5±0.4	3.5±0.4	p<0,05

In Group I, the average ovarian volume increased to 5.5±1.0 cm^3, closer to the normal range (6-8 cm^3). Normal ovarian volume was restored in 82% of patients. The average endometrial thickness increased to 7.0±1.0 mm, significantly closer to normal values (8-12 mm in the secretory phase). The endometrium was within normal limits in 80% of patients. Ovulatory dysfunction was reduced, with only 30% of patients showing signs of dysfunction, manifested by the absence of dominant follicles and cyst formation.

In Group II, the average ovarian volume increased to 6.0±1.1 cm^3, within the normal range. Normal ovarian volume was restored in 80% of patients. The average endometrial thickness increased to 8.0±1.0 mm, within normal values. The endometrium was within normal limits in 78% of patients. Ovulatory disorders were identified in 10% of patients, including the absence of dominant follicles and the presence of small cystic changes.

Thus, ultrasound studies after 3 months of Tyramine therapy showed positive changes in the structure and functionality of the thyroid gland and pelvic organs in patients with hypothyroidism and hyperthyroidism. The reduction in thyroid gland size, improvement in its structure and decreased vascularization, as well as improvements in ovarian and endometrial parameters, confirm the effectiveness of Tyramine therapy and its positive impact on menstrual and reproductive functions in women.

In patients with hypothyroidism, Tyramine treatment contributed to the restoration of regular menstrual function in 83.4% and pregnancy in 83%, while in patients with hyperthyroidism, the menstrual cycle normalized in 84.3% and pregnancy occurred in 84.5% of women (see Fig. 4).

Thus, the study results confirm the significant role of thyroid dysfunction in the development of endocrine infertility in women and the effectiveness of modern treatment methods aimed at restoring reproductive function.

4. Discussion

In this study, clinical, laboratory, and instrumental indicators were assessed in women with endocrine infertility caused by thyroid dysfunction. The main objective was to identify the impact of hypothyroidism and hyperthyroidism on reproductive function and evaluate the effectiveness of Tyramine treatment.

The results of the hormonal study before treatment showed significant changes in thyroid hormone levels in patients with hypothyroidism and hyperthyroidism. Women with hypothyroidism had significantly elevated TSH levels and reduced free T4 and T3 levels, indicating insufficient thyroid function. The high TPO-Ab level in most patients suggests a possible autoimmune nature of the disease. Women with hyperthyroidism showed the opposite pattern: high levels of free T4 and T3, and low TSH levels, indicating hyperthyroid function. The elevated TPO-Ab level also indicates a possible autoimmune origin of the disease.

Ultrasound examination of the thyroid gland before treatment revealed an increase in its size in most patients with thyroid dysfunction, which is associated with compensatory and inflammatory processes. These changes included structural heterogeneity and vascularization changes, confirming the presence of an active pathological process in the gland.

Instrumental studies of the pelvic organs before treatment showed the negative impact of thyroid dysfunction on the reproductive system. Patients with hypothyroidism and hyperthyroidism had reduced ovarian volume and endometrial thickness, which is a significant factor in the development of endocrine infertility. Ovulatory dysfunctions, manifested by the absence of dominant follicles and cyst formation, were also identified in a significant number of patients.

Tyramine therapy proved effective in normalizing thyroid hormone and thyroid peroxidase antibody levels. After 3 months of treatment, patients with hypothyroidism showed a significant decrease in TSH levels and an increase in free T4 and T3 levels. The TPO-Ab level also decreased, indicating a reduction in autoimmune inflammation. Patients with hyperthyroidism showed a decrease in free T4 and T3 levels and an increase in TSH levels, indicating normalization of thyroid function. The TPO-Ab level also decreased, confirming a reduction in the autoimmune process.

Ultrasound studies after treatment showed positive changes in the structure and functionality of the thyroid gland and pelvic organs. The reduction in thyroid gland size, improvement in its structure, decreased vascularization, and increased ovarian volume and endometrial thickness confirm the effectiveness of the therapy. Most patients restored regular menstrual function, and a significant number of women achieved pregnancy, indicating the restoration of reproductive function.

Thus, this study confirms the significant role of thyroid dysfunction in the development of endocrine infertility in women. Tyramine treatment has shown high effectiveness in normalizing hormonal profiles and improving reproductive

function in patients with hypothyroidism and hyperthyroidism. These data underscore the necessity of timely diagnosis and treatment of thyroid dysfunction to improve women's reproductive health.

5. Conclusions

Our study has shown that thyroid dysfunction plays an important role in the development of endocrine infertility in women, significantly impacting their reproductive function. Hypothyroidism and hyperthyroidism lead to serious hormonal imbalances, adversely affecting the menstrual cycle, ovulation, and overall fertility. The use of Tyramine has demonstrated high effectiveness in normalizing thyroid hormone levels, improving clinical outcomes, and restoring reproductive function in 84.5% of patients with thyroid dysfunction. Tyramine treatment led to significant improvement in hormonal indicators in women with hypothyroidism and hyperthyroidism, as evidenced by decreased TSH levels and normalization of free T4 levels. In patients with hypothyroidism, Tyramine treatment contributed to the restoration of regular menstrual function in 83.4% and pregnancy in 83%, while in patients with hyperthyroidism, the menstrual cycle normalized in 84.3% and pregnancy occurred in 84.5% of women.

Overall, our study highlights the importance of early diagnosis and timely correction of thyroid dysfunction to improve women's reproductive health. The use of modern treatment methods, including Tyramine, provides effective means for restoring hormonal balance and reproductive function in women with endocrine infertility. These findings confirm the need for further research in this area to develop more effective and individualized treatment methods.

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