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THE SPECTRUM OF REPRODUCTIVE DISORDERS IN WOMEN WITH SUBCLINICAL AND OVERT HYPOTHYROIDISM

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ABSTRACT

Objective. To investigate the spectrum of reproductive disorders in women with subclinical and overt hypothyroidism.

Materials and methods. Reproductive health characteristics were assessed in 51 women with stage I–II diffuse goiter and hypothyroidism who sought medical care for menstrual irregularities at the Kashkadarya Branch of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Yo.Kh. Turakulov, Ministry of Health of the Republic of Uzbekistan, during 2025. The control group comprised 20 healthy women without menstrual irregularities. Participants were divided into three groups: Group 1 included 23 women with subclinical hypothyroidism; Group 2 included 28 women with overt hypothyroidism; and Group 3 was the control group of 20 healthy women.

Results. All 51 patients (100%) were aged 18–44 years. Grade 1 obesity was the most common category, affecting 22 women (43.1%); 18 women (35.3%) were overweight, and 11 (21.6%) had grade 2 obesity. In Group 1, a non-significant reduction in pituitary and ovarian hormone levels was observed in the setting of normoprolactinemia and normoandrogenemia. On day 14 of the menstrual cycle, LH, FSH, estradiol, and progesterone levels were lower than those in the control group; these differences were not statistically significant ($p > 0.05$). In Group 2, a significant reduction in pituitary and ovarian hormone levels was observed alongside marked hyperprolactinemia and impaired ovarian function. Compared with controls, LH and FSH levels on cycle day 14 were significantly lower, whereas free testosterone levels were higher ($p < 0.05$).

Conclusions. The most pronounced menstrual disturbances were observed in women with overt hypothyroidism. The manuscript reports that grade 2 obesity was more frequent in Group 2, affecting 30 of 51 patients (58.8%).

KEYWORDS

Hypothyroidism; women; diffuse goiter.

Introduction

Thyroid diseases include autoimmune thyroid diseases (AITDs), goiter, thyroid nodules, and thyroid cancer. The main AITDs are autoimmune thyroiditis and Graves' disease. A common feature of thyroid disorders is their predominance among women. The female-to-male ratio is 4–6:1 for AITDs and approximately 3–4:1 for thyroid nodules. For papillary thyroid carcinoma (PTC), this ratio is highest during the reproductive years, decreasing from five or more in patients aged 20–24 years to 3.4 in those aged 35–44 years and to one in patients over 80 years of age. The effects of female gonadal hormones and X-chromosome inactivation on the thyroid gland and immune system contribute substantially to women's predisposition to AITDs. The principal hormonal factors include prolactin and estrogen. The direct effects of estrogen on thyroid tissue may contribute to the development of goiter, thyroid nodules, and thyroid cancer in women [1].

Hypothyroidism is an endocrine disorder characterized by insufficient production of thyroid hormones (THs) and is substantially more prevalent in women. Its pathophysiology is influenced by genetic, hormonal, and environmental factors, including nutritional disturbances. Several micronutrients, such as iodine, iron, selenium, zinc, and vitamin D, play key roles in TH synthesis, peripheral conversion, and action. Women may be more vulnerable to deficiencies in these nutrients because of their specific nutritional requirements, increasing their susceptibility to thyroid dysfunction, particularly during pregnancy and the postpartum period. Current evidence supports assessing nutritional status as an adjunct to conventional levothyroxine (LT4) therapy, particularly in women with subclinical hypothyroidism or autoimmune thyroid disease. Appropriate nutritional interventions may play an important role in improving treatment effectiveness and disease control [2].

Thyroid disorders are common endocrine conditions that affect multiple organ systems, including the reproductive system, and may lead to sexual dysfunction. The effects may differ by sex; for example, women with hypothyroidism often report reduced libido. Low thyroid hormone levels have also been associated with vaginal dryness, which may cause discomfort, particularly during sexual intercourse. A study aimed to assess the global prevalence of sexual dysfunction in women with thyroid disorders [3]. The substantial prevalence reported in this population highlights the need to increase awareness. Targeted educational initiatives may help reduce the occurrence of sexual dysfunction and its adverse effects, thereby improving affected women's overall quality of life.

A systematic search of electronic databases, including PubMed, Scopus, Web of Science, Embase, ScienceDirect, and Google Scholar, was conducted to identify studies reporting the prevalence of sexual dysfunction in patients with thyroid disorders through February 8, 2024. An analysis of nine studies involving a total of 1,013 participants found that the overall prevalence of sexual dysfunction among women with thyroid disorders was 44.8% (95% CI: 33.8–56.2). A subgroup analysis was performed because of the substantial number of reports concerning women with hypothyroidism or hyperthyroidism. The prevalence of sexual dysfunction was 41.8% (95% CI: 26.3–59.0) among women with hypothyroidism and 59.6% (95% CI: 50.5–68.1) among women with hyperthyroidism [3].

According to the authors, thyroid dysfunction during pregnancy is associated with adverse outcomes for both the mother and the fetus. A meta-analysis was conducted to assess thyroid dysfunction among pregnant women in Iran. Nineteen eligible studies involving 17,670 pregnant women were included. The prevalence of thyroid dysfunction among pregnant women in Iran was 18.10% (95% CI: 13.89–

23.25). The respective prevalence estimates for hypothyroidism, clinical hypothyroidism, and subclinical hypothyroidism were 13.01% (95% CI: 9.15–18.17), 1.35% (95% CI: 0.97–1.86), and 11.90% (95% CI: 7.40–18.57). The prevalence estimates for hyperthyroidism, clinical hyperthyroidism, and subclinical hyperthyroidism were 3.31% (95% CI: 1.62–6.61), 1.06% (95% CI: 0.61–1.84), and 2.56% (95% CI: 0.90–7.05), respectively. The prevalence of thyroid peroxidase antibodies was estimated at 11.68% (95% CI: 7.92–16.89) [4].

Severe thyroid dysfunction may lead to menstrual disturbances and subfertility. Fertility problems may persist even after thyroid function has been restored; in such cases, assisted reproductive technologies (ART) may be considered. Ovarian stimulation before ART increases estradiol levels, which may induce hypothyroidism in women with autoimmune thyroid disease (AITD), necessitating levothyroxine (LT4) treatment before pregnancy. In addition, AITD is more common among women with polycystic ovary syndrome and idiopathic subfertility [5]. In women with TSH levels above 4.0 mIU/L, fertilization outcomes and embryo quality may be impaired; these parameters may improve with LT4 therapy. Meta-analyses, which predominantly included women with TSH levels above 4.0 mIU/L, reported an increased live-birth rate with LT4 treatment. However, this benefit was not confirmed in two recent interventional studies involving euthyroid women with thyroid autoimmunity [5].

Female infertility is defined as the inability to achieve pregnancy after one year of regular unprotected sexual intercourse. Among the various endocrine factors contributing to this complex condition, thyroid dysfunction plays an important role [6]. A review of 134 articles published up to 2023 was conducted using the PubMed/MEDLINE, EMBASE, and SciELO databases. The primary aim of that review was to examine the impact of thyroid dysfunction on female infertility.

Thyroid hormones play a vital role in the complex functioning of the female reproductive system by regulating metabolism and coordinating the growth of ovarian and uterine tissues [7]. Their essential contribution extends to key reproductive processes, including folliculogenesis, fertilization, embryogenesis, and implantation [8]. Menstrual-cycle regularity, which results from a cascade of interconnected signals within the hypothalamic–pituitary–ovarian axis, may be disrupted in patients with thyroid disease.

These considerations provided the rationale for the present study.

Aim of the study

To investigate the spectrum of reproductive disorders in women with subclinical and overt hypothyroidism.

Materials and methods

The reproductive health characteristics of 51 women with stage I–II diffuse goiter and hypothyroidism who presented with menstrual irregularities to the Kashkadarya Branch of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Yo.Kh. Turakulov, Ministry of Health of the Republic of Uzbekistan, during 2025 were studied. The control group consisted of 20 healthy women without menstrual irregularities.

Participants were allocated to three groups according to thyroid functional status: Group 1 comprised 23 patients with subclinical hypothyroidism; Group 2 comprised 28 patients with overt hypothyroidism; and Group 3 comprised 20 healthy controls.

The age of patients in Group 1 ranged from 20 to 39 years, with a mean age of 28.3 ± 0.64 years. In Group 2, the age range was 22–37 years, with a mean of 30.4 ± 0.51 years. The mean age in Group 3 was 29.4 ± 0.51 years.

Inclusion criteria: primary hypothyroidism; female sex; reproductive age.

Exclusion criteria: hyperthyroidism; women older than 44 years.

All patients underwent the following investigations: general clinical and biochemical tests, including complete blood count, urinalysis, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin; hormonal blood tests, including thyroid-stimulating hormone (TSH), free thyroxine, antibodies to the TSH receptor (TRAb), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, and free testosterone, measured on days 7, 14, and 21 of the menstrual cycle; electrocardiography (ECG); and ultrasonography of the uterus and ovaries, with folliculometry on cycle day 14. An oral glucose tolerance test was performed when indicated.

The data were processed using Microsoft Excel and STATISTICA 6. Mean values (M) and standard errors of the mean (m) were calculated. Between-group differences were assessed using confidence intervals and Student's t-test (p). Differences were considered statistically significant at $p < 0.05$.

Results

Table 1 presents the distribution of patients by age and study group. All 51 patients (100%) were within the 18–44-year age category.

Table 1. Distribution of participants by age and study group (WHO age categories).

Age, years	Group 1 (n = 23)	Group 2 (n = 28)	Group 3 (n = 20)
18–44	23	28	20
45–59	—	—	—
60–74	—	—	—
75 and older	—	—	—
Total	23	28	20

Table 2 presents the anthropometric data for the groups before treatment.

Table 2. Mean body mass index (BMI) values by group.

Group	Overweight (BMI 25.0–29.9 kg/m²), n; mean ± SD	Grade 1 obesity (BMI 30.0–34.9 kg/m²), n; mean ± SD	Grade 2 obesity (BMI 35.0–39.9 kg/m²), n; mean ± SD
Group 1	5; 33.5 ± 3.8	8; 33.8 ± 3.2	4; 36.2 ± 4.6
Group 2	9; 34.3 ± 4.5	14; 34.6 ± 4.1	7; 38.3 ± 3.5
Total	18	22	11

As shown in Table 2, grade 1 obesity was the most common category, affecting 22 patients (43.1%). Overweight was observed in 18 patients (35.3%), while grade 2 obesity was found in 11 patients (21.6%). Grade 2 obesity was more common in Group 2.

Table 3 shows the frequency of various neuroendocrine and menstrual disorders in the study groups.

Table 3. Frequency of menstrual disorders by group.

Disorder	Group 1 (n = 23)	Group 2 (n = 28)
Secondary amenorrhea	2 (8.69%)	15 (53.6%)*
Primary amenorrhea	—	6 (21.4%)
Hyperpolymenorrhea	3 (13.04%)	10 (35.7%)*
Opsomenorrhea	6 (26.0%)	9 (32.1%)
Oligomenorrhea	6 (26.0%)	9 (32.1%)
Anovulation	2 (8.69%)	15 (53.6%)*
Hypoovulatory syndrome	3 (13.04%)	9 (32.1%)
Primary infertility	4 (17.39%)	12 (42.9%)*
Secondary infertility	2 (8.69%)	5 (17.9%)

Note: * p-value indicates a statistically significant difference compared with Group 1.
As shown in Table 3, menstrual disorders were more prevalent in Group 2 than in Group 1. The most frequent disorders in Group 2 were secondary amenorrhea (15 patients; 53.6%), hyperpolymenorrhea (10; 35.7%), anovulation (15; 53.6%), and primary infertility (12; 42.9%).
For a more detailed analysis, statistical comparisons of mean basal plasma hormone levels on day 14 of the menstrual cycle were performed in both patient groups. The results are presented in Tables 4 and 5.

Table 4. Mean basal plasma hormone levels on cycle day 14 in Group 1 before treatment.

Hormone	Mean value	p-value	Control	Reference range
LH	18.8 ± 2.4	>0.05	21.3 ± 2.1	14–95 mIU/mL (ovulation)
FSH	14.1 ± 2.3	>0.05	16.5 ± 1.3	5.8–21.0 mIU/mL (ovulation)
Prolactin	5.5 ± 0.3	>0.05	4.3 ± 0.5	4.1–30 ng/mL
Free testosterone	0.3 ± 0.02	>0.05	0.2 ± 0.05	0.2–1.0 ng/mL
Progesterone	32.5 ± 3.5	<0.05	44.3 ± 9.3	11–80 nmol/L
Estradiol	0.31 ± 0.04	>0.05	1.7 ± 0.01	0.34–1.8 nmol/L

Note: p-values indicate differences compared with the control group.
As shown in Table 4, Group 1 patients demonstrated a non-significant decrease in both pituitary and ovarian hormone levels in the presence of normoprolactinemia and normoandrogenemia. Compared with the control group, LH and FSH levels on cycle day 14 were slightly lower but remained within the reference range; estradiol and progesterone levels were also lower. According to the narrative description, these differences were not statistically significant ($p > 0.05$).
In Group 2, a statistically significant decrease in both pituitary and ovarian hormone levels was also reported, accompanied by marked hyperprolactinemia and an evident reduction in ovarian function. Compared with controls, LH and FSH levels on cycle day 14 were significantly lower, whereas free testosterone levels were higher ($p < 0.05$).

Table 5. Mean basal plasma hormone levels on cycle day 14 in Group 2 before treatment.

Hormone	Mean value	p-value	Control	Reference range
LH	6.7 ± 0.3	<0.05	21.3 ± 2.1	14–95 mIU/mL (ovulation)
FSH	4.2 ± 0.2	<0.05	16.5 ± 1.3	5.8–21.0 mIU/mL (ovulation)
Prolactin	27.8 ± 1.6	<0.05	4.3 ± 0.5	4.1–30 ng/mL
Free testosterone	2.5 ± 0.2	<0.05	0.2 ± 0.05	0.2–1.0 ng/mL
Progesterone	12.5 ± 3.5	<0.05	44.3 ± 9.3	11–80 nmol/L
Estradiol	0.22 ± 0.04	<0.01	1.7 ± 0.01	0.34–1.8 nmol/L

Note: p-values indicate differences compared with the control group.

Thus, the most pronounced disturbances in the hypothalamic–pituitary–ovarian axis were identified in Group 2, which comprised patients with overt hypothyroidism. These patients showed a statistically significant reduction in pituitary–gonadal function, specifically lower plasma LH, FSH, estradiol, and progesterone levels on day 14 of the menstrual cycle. These findings were supported by uterine and ovarian ultrasonography, which demonstrated a reduced ovarian follicular reserve and anovulation.

Conclusions

1. The most pronounced menstrual disturbances were observed in patients with overt hypothyroidism. Menstrual disorders were more prevalent in Group 2 than in Group 1. The most frequent conditions in Group 2 were secondary amenorrhea (15 patients; 53.6%), hyperpolymenorrhea (10; 35.7%), anovulation (15; 53.6%), and primary infertility (12; 42.9%).
2. The manuscript states that grade 2 obesity was more common in Group 2, affecting 30 of the 51 patients (58.8%).

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Editorial points requiring author verification

The following discrepancies are present in the source manuscript and have been retained without correction in this translation:

- The abstract and conclusion state that grade 2 obesity affected 30 of 51 patients (58.8%), whereas Table 2 reports 11 patients (21.6%) overall and 7 patients in Group 2.
- The abstract describes the hormone changes in Group 1 as non-significant ($p > 0.05$), but Table 4 lists progesterone at $p < 0.05$.
- The narrative description of Group 2 refers to “marked hyperprolactinemia”; the reported mean prolactin value is 27.8 ± 1.6, while the reference interval in the table is 4.1–30 ng/mL.
- The manuscript describes a significant decrease in ovarian hormones in Group 2; however, free testosterone is reported as increased. This has been translated as reported in the source.
- The source alternates between “diffuse goiter stage I–II” and hypothyroidism without specifying the diagnostic criteria or laboratory thresholds used to define subclinical and overt hypothyroidism.
- The reference list entries 7 and 8 are incomplete in the source and should be completed with full bibliographic details.