Assessment Of The Impact Of Micronutrient Status On Female Reproductive Health In Subclinical Thyroid Dysfunction

Zokirova D.D Department of Hospital Therapy and Endocrinology Andijan State Medical Institute

Yusupova Sh.Q. Department of Hospital Therapy and Endocrinology Andijan State Medical Institute

ABSTRACT

Subclinical thyroid dysfunction is a common endocrine disorder among women of reproductive age and may negatively affect menstrual function, ovarian reserve, fertility, and pregnancy outcomes. Micronutrients, particularly selenium, iron, zinc, and vitamin D, play essential roles in thyroid hormone synthesis, metabolism, antioxidant defense, and regulation of the hypothalamic–pituitary–ovarian axis. However, the combined relationship between micronutrient status, thyroid function, reproductive hormonal profile, and ovarian reserve in women with subclinical thyroid dysfunction remains insufficiently studied.

Objective. To assess the impact of micronutrient status on thyroid function, reproductive hormonal profile, ovarian reserve, and selected parameters of reproductive health in women of reproductive age with subclinical thyroid dysfunction.

Materials and Methods. The study included women aged 18–40 years who were divided into three groups according to thyroid functional status: women with subclinical hypothyroidism, women with subclinical hyperthyroidism, and euthyroid controls. Thyroid status was assessed by serum thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), anti-thyroid peroxidase antibodies (anti-TPO), and anti-thyroglobulin antibodies (anti-TG). Reproductive hormonal assessment included follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, prolactin, and anti-Müllerian hormone (AMH). Micronutrient status was evaluated by measuring selenium, iron, zinc, and vitamin D levels. Thyroid ultrasonography and pelvic ultrasound were performed to assess structural thyroid changes and ovarian morphology.

Results. Women with subclinical thyroid dysfunction demonstrated alterations in micronutrient status compared with euthyroid controls. Reduced concentrations of selenium, iron, zinc, and vitamin D were associated with less favorable thyroid and reproductive hormonal profiles. In women with subclinical hypothyroidism, micronutrient deficiencies tended to be associated with higher TSH concentrations, disturbances in gonadotropin and prolactin levels, menstrual abnormalities, and lower markers of ovarian reserve. Alterations in thyroid function and micronutrient status were also associated with changes in AMH and ovarian ultrasound parameters. The relationship between micronutrient deficiency and reproductive dysfunction was more pronounced in women with concomitant thyroid autoimmunity.

Conclusion. Micronutrient imbalance may represent an important modifying factor in the development of reproductive disorders in women with subclinical thyroid dysfunction. Assessment of selenium, iron, zinc, and vitamin D status together with thyroid and reproductive hormonal parameters may improve the identification of women at increased risk of impaired ovarian function and reduced reproductive potential.

Keywords:	subclinical hypothyroidism, subclinical hyperthyroidism, thyroid dysfunction, micronutrients, selenium, zinc, iron, vitamin D, ovarian reserve, anti-Müllerian hormone, reproductive health, women.

INTRODUCTION / RELEVANCE

Thyroid disorders are among the most common endocrine abnormalities affecting women of reproductive age. Even mild alterations in thyroid function may influence menstrual cyclicity, ovulation, fertility, ovarian reserve, and the course of pregnancy. Subclinical thyroid dysfunction is characterized by abnormal serum thyroid-stimulating hormone concentrations with circulating free thyroid hormone levels remaining within the reference range.

Subclinical hypothyroidism is generally characterized by an elevated TSH concentration with normal fT4 levels, whereas subclinical hyperthyroidism is characterized by decreased TSH with normal circulating fT4 and fT3 concentrations. Because clinical manifestations may be mild or absent, these conditions can remain undiagnosed for a prolonged period.

The thyroid gland and female reproductive system are closely interconnected through complex endocrine mechanisms. Thyroid hormones affect the hypothalamic–pituitary–ovarian axis, ovarian folliculogenesis, steroidogenesis, endometrial function, and reproductive hormone metabolism. Therefore, even subclinical disturbances in thyroid homeostasis may contribute to menstrual irregularities, anovulation, infertility, and changes in ovarian reserve.

An additional factor that may influence this relationship is micronutrient status. Adequate availability of selenium, iron, zinc, and vitamin D is important for normal thyroid physiology and reproductive function.

Selenium is an essential component of selenoproteins, including iodothyronine deiodinases and antioxidant enzymes. Deiodinases are responsible for the peripheral conversion and metabolism of thyroid hormones, while selenium-dependent antioxidant systems protect thyroid tissue from oxidative stress.

Iron is essential for multiple enzymatic processes and is required for normal thyroid hormone synthesis. Iron deficiency may impair thyroid peroxidase activity and can simultaneously affect reproductive function through anemia, tissue hypoxia, and altered ovarian physiology.

Zinc participates in the regulation of thyroid hormone metabolism, receptor function, DNA transcription, and reproductive hormone activity. Zinc deficiency may therefore contribute to disturbances in both thyroid and gonadal function.

Vitamin D has immunomodulatory and endocrine effects and has attracted particular attention because vitamin D insufficiency has been reported in association with autoimmune thyroid disorders and several reproductive abnormalities. Vitamin D receptors are expressed in reproductive tissues, including the ovary and endometrium, suggesting a potential role in folliculogenesis and reproductive function.

Despite the established biological importance of individual micronutrients, the integrated relationship between micronutrient status, subclinical thyroid dysfunction, reproductive hormone levels, and ovarian reserve remains incompletely understood. A comprehensive assessment of these parameters may provide additional opportunities for identifying women at risk of reproductive dysfunction and for developing individualized preventive and therapeutic approaches.

OBJECTIVE

The aim of this study was to assess the relationship between micronutrient status and reproductive health in women of reproductive age with subclinical thyroid dysfunction.

The specific objectives were to:

1. evaluate serum selenium, iron, zinc, and vitamin D concentrations in women with subclinical hypothyroidism and subclinical hyperthyroidism;
2. assess thyroid functional and autoimmune parameters, including TSH, fT4, fT3, anti-TPO, and anti-TG;

3. investigate reproductive hormonal profiles using FSH, LH, estradiol, progesterone, prolactin, and AMH;
4. assess ovarian reserve and ovarian morphology using biochemical and ultrasound parameters;
5. determine the relationship between micronutrient deficiencies and thyroid dysfunction;
6. evaluate associations between micronutrient status, thyroid parameters, and indicators of female reproductive function.

MATERIALS AND METHODS

Study Design and Participants

A clinical observational study was conducted among women of reproductive age. A total of 150 women aged 18–40 years were included in the study.

According to thyroid functional status, the participants were divided into three groups:

Group I: women with subclinical hypothyroidism;

Group II: women with subclinical hyperthyroidism;

Group III: euthyroid women without evidence of subclinical thyroid dysfunction, who served as the control group.

The diagnosis of subclinical thyroid dysfunction was established on the basis of serum TSH and free thyroid hormone concentrations.

Inclusion Criteria

The main inclusion criteria were reproductive age between 18 and 40 years, confirmed subclinical thyroid dysfunction for the study groups, preserved ability to undergo reproductive hormonal assessment, and informed consent to participate in the study.

Exclusion Criteria

Women with overt hypothyroidism or hyperthyroidism, pregnancy, severe systemic diseases, active malignant disease, severe hepatic or renal dysfunction, and other conditions capable of substantially influencing thyroid or reproductive hormonal parameters were excluded from the study.

Laboratory Assessment

Venous blood samples were collected for biochemical and hormonal evaluation.

Thyroid function was assessed using:

- thyroid-stimulating hormone (TSH);
- free thyroxine (fT4);
- free triiodothyronine (fT3);
- anti-thyroid peroxidase antibodies (anti-TPO);
- anti-thyroglobulin antibodies (anti-TG).

Reproductive hormonal status was evaluated by measuring:

- follicle-stimulating hormone (FSH);
- luteinizing hormone (LH);
- estradiol;
- progesterone;
- prolactin;
- anti-Müllerian hormone (AMH).

AMH was used as one of the principal biochemical markers of ovarian reserve.

Assessment of Micronutrient Status

The following micronutrients were evaluated:

- selenium (Se);
- iron (Fe);
- zinc (Zn);
- vitamin D [25-hydroxyvitamin D, 25(OH)D].

Micronutrient concentrations were analyzed in relation to thyroid functional parameters, reproductive hormone levels, ovarian reserve, and clinical manifestations of reproductive dysfunction.

Ultrasound Examination

All participants underwent thyroid ultrasonography to assess thyroid volume, echogenicity, structural abnormalities, and features suggestive of autoimmune thyroid disease.

Pelvic ultrasonography was performed to evaluate ovarian morphology, follicular characteristics, and other structural parameters relevant to reproductive function.

Statistical Analysis

Statistical analysis was performed using appropriate descriptive and inferential statistical methods. Continuous variables were expressed as mean ± standard deviation or median with interquartile range depending on data distribution.

Differences between groups were assessed using parametric or non-parametric tests as appropriate. Correlation analysis was performed to investigate relationships between micronutrient concentrations, thyroid parameters, reproductive hormones, and ovarian reserve indicators.

A p-value <0.05 was considered statistically significant.

RESULTS

The comparative analysis demonstrated differences in micronutrient status between women with subclinical thyroid dysfunction and euthyroid controls.

Women with subclinical hypothyroidism showed a tendency toward lower serum concentrations of selenium, zinc, iron, and vitamin D. Micronutrient deficiencies were more frequently observed among women with biochemical evidence of thyroid autoimmunity.

An inverse relationship was observed between TSH concentration and several indicators of micronutrient sufficiency. Lower selenium status was associated with less favorable thyroid functional parameters, supporting the potential role of selenium-dependent deiodinases and antioxidant mechanisms in maintaining thyroid hormone homeostasis.

Iron deficiency was associated with changes in thyroid function and reproductive parameters. Women with reduced iron status more frequently demonstrated menstrual disturbances and less favorable reproductive hormonal profiles.

Reduced zinc concentrations were associated with alterations in thyroid hormone metabolism and reproductive hormonal balance. These findings suggest that zinc status may influence both thyroid and ovarian function through multiple enzymatic and receptor-mediated mechanisms.

Vitamin D insufficiency or deficiency was frequently detected among women with subclinical thyroid dysfunction, particularly in those with markers of autoimmune thyroid disease. Lower vitamin D concentrations were associated with a less favorable endocrine profile.

Analysis of reproductive hormones revealed that women with subclinical thyroid dysfunction had more pronounced alterations in FSH, LH, estradiol, progesterone, and prolactin compared with euthyroid controls.

Particular attention was given to AMH as a marker of ovarian reserve. Women with combined thyroid dysfunction and micronutrient deficiencies tended to have lower AMH levels and less favorable ovarian ultrasound characteristics compared with women with adequate micronutrient status.

Correlation analysis indicated significant relationships between selected micronutrient concentrations and thyroid and reproductive parameters. The combination of subclinical thyroid dysfunction and multiple micronutrient deficiencies was associated with a greater degree of reproductive hormonal disturbance than isolated changes in thyroid function.

These findings indicate that micronutrient status may act as an important modifying factor linking subclinical thyroid dysfunction with impaired reproductive function.

DISCUSSION

The results of the present study demonstrate a close relationship between micronutrient status, thyroid homeostasis, and reproductive function in women of reproductive age.

The observed association between selenium deficiency and thyroid dysfunction can be explained by the biological role of selenium-containing enzymes in thyroid hormone metabolism. Selenium-dependent iodothyronine deiodinases participate in the activation and inactivation of thyroid hormones, whereas glutathione peroxidases protect thyroid tissue from oxidative damage.

Iron deficiency may additionally contribute to impaired thyroid hormone synthesis because thyroid peroxidase is a heme-dependent enzyme. Consequently, insufficient iron availability may affect thyroid hormone production and aggravate functional thyroid abnormalities.

Zinc plays an important role in transcriptional regulation, receptor signaling, antioxidant defense, and endocrine function. Therefore, inadequate zinc status may influence both the thyroid gland and reproductive system.

Vitamin D may be particularly relevant in women with autoimmune thyroid disease. Its

immunomodulatory properties and the presence of vitamin D receptors in reproductive tissues provide a biological basis for an association between vitamin D deficiency, thyroid autoimmunity, and reproductive dysfunction.

The relationship between thyroid dysfunction and ovarian reserve is of particular clinical importance. AMH reflects the functional ovarian follicular pool and is widely used as a marker of ovarian reserve. The association between micronutrient deficiencies, altered thyroid status, and lower AMH values suggests that evaluation of thyroid function alone may not fully characterize endocrine factors influencing reproductive potential.

Thus, a comprehensive diagnostic approach combining thyroid hormones, thyroid autoantibodies, reproductive hormones, ovarian reserve markers, micronutrient status, and ultrasound findings may provide a more complete assessment of reproductive risk in women with subclinical thyroid dysfunction.

CONCLUSIONS

1. Subclinical thyroid dysfunction in women of reproductive age is associated with alterations in reproductive hormonal status and may negatively affect ovarian function and reproductive potential.
2. Deficiencies or insufficient levels of selenium, iron, zinc, and vitamin D are frequently associated with less favorable thyroid functional parameters.
3. Micronutrient imbalance may contribute to disturbances in the hypothalamic–pituitary–ovarian axis and may be associated with changes in FSH, LH, estradiol, progesterone, prolactin, and AMH.
4. Women with concomitant thyroid autoimmunity and micronutrient deficiencies may represent a subgroup with a higher risk of reproductive endocrine disturbances.
5. Combined assessment of TSH, fT4, fT3, anti-TPO, anti-TG, reproductive hormones, AMH, selenium, iron, zinc, and vitamin D may improve the evaluation of reproductive health in women with subclinical thyroid dysfunction.
6. Assessment and appropriate correction of micronutrient deficiencies may represent a potentially important component of an individualized approach to women with subclinical thyroid dysfunction; however, the clinical benefits of supplementation should be evaluated separately and should not be inferred solely from observational associations.
7. Further prospective studies are required to determine whether correction of micronutrient deficiencies can improve thyroid homeostasis, ovarian reserve, menstrual function, and fertility outcomes in this patient population.

REFERENCES

1. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315–389. doi:10.1089/thy.2016.0457.
2. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA. 2019;322(2):153–160. doi:10.1001/jama.2019.9052.
3. Delitala AP, Capobianco G, Cherchi PL, Dessole S, Delitala G. Thyroid function and thyroid disorders during pregnancy: a review and care pathway. Arch Gynecol Obstet. 2019;299(2):327–338. doi:10.1007/s00404-018-5018-8.
4. Rayman MP. Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. Proc Nutr Soc. 2019;78(1):34–44. doi:10.1017/S0029665118001192.
5. Duntas LH. Selenium and the thyroid: a close-knit connection. J Clin Endocrinol Metab. 2010;95(12):5180–5188. doi:10.1210/jc.2010-0191.

6. Zimmermann MB, Köhrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid. 2002;12(10):867–878. doi:10.1089/105072502761016494.
7. Muscogiuri G, Tirabassi G, Bizzaro G, Orio F, Paschou SA, Vryonidou A, et al. Vitamin D and thyroid disease: to D or not to D? Eur J Clin Nutr. 2015;69(3):291–296. doi:10.1038/ejcn.2014.265.
8. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010;31(5):702–755. doi:10.1210/er.2009-0041.
9. Mintziori G, Kita M, Duntas L, Goulis DG. Consequences of hyperthyroidism in male and female fertility: pathophysiology and current management. J Endocrinol Invest. 2016;39(8):849–853. doi:10.1007/s40618-016-0452-6.
10. Poppe K, Velkeniers B, Glinoer D. Thyroid disease and female reproduction. Clin Endocrinol (Oxf). 2007;66(3):309–321. doi:10.1111/j.1365-2265.2007.02752.x.