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ORIGINAL RESEARCH

Thyroid Hormone in Women with Premature Ovarian Insufficiency: A Case-Control Study

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Purpose: To compare thyroid function in patients with premature ovarian insufficiency (POI) with control women of reproductive age and to look into the potential association between thyroid function and metabolic markers in POI patients.

Patients and Methods: This cross-sectional case-control study enrolled 227 initially diagnosed POI patients and 232 controls with regular menstrual periods, all aged 20–40 years. Serum levels of thyroid hormones were compared between the two groups. In women with POI, further correlation analysis of thyroid function with sex hormones and metabolic markers was conducted.

Results: Women with POI exhibited higher serum concentrations of free triiodothyronine (FT_3) (4.43 ± 0.55 pmol/L vs 4.22 ± 0.48 pmol/L, $P < 0.001$), free thyroxine (FT_4) (14.07 [12.93, 15.37] pmol/L vs 13.11 [12.31, 13.87] pmol/L, $P < 0.001$), and a higher proportion of thyrotropin (TSH) ≥ 2.5 mIU/L (22.47% vs 15.09%, $P = 0.043$) than controls, with all values remaining within the normal reference range. Elevated serum levels of FT_3 and FT_4 were positively associated with POI. In POI patients, weak positive correlations of blood glucose with both FT_3 and FT_4 were observed, whereas no significant associations were found with other metabolic markers.

Conclusion: This study indicated that higher levels of thyroid hormones, with statistically significant but clinically subtle differences within normal ranges, were positively associated with POI. In women with POI, thyroid hormone levels also showed a weak positive correlation with blood glucose. Further investigation is needed to clarify the clinical significance of these findings.

Keywords: premature ovarian insufficiency, thyroid hormones, metabolic markers, correlation

Introduction

Premature ovarian insufficiency (POI) is a clinical condition defined as ovarian function loss before the age of 40,[1] which is characterized by menstrual disorders (amenorrhea or oligomenorrhea), low estradiol levels, and elevated gonadotropin levels.[2,3] The prevalence of POI has been increasing during the last 20 years, with an overall prevalence of 3.5% among women globally and 5.3% in developing countries.[4] Numerous studies have shown that POI could result in a variety of implications on physical and psychological health,[3] as well as the quality of life,[5] owing to early deprivation of estrogen levels. Approximately 90% of POIs have an unestablished etiology, which may include genetic, iatrogenic, and autoimmune factors. A proportion of 4–30% of POI cases is thought to be caused by autoimmune diseases, of which thyroid-related diseases possibly have the strongest correlation with POI.[6,7]

Thyroid hormones, as commonly acknowledged, possess a diverse array of physiological functions and play a fundamental role in the endocrine system, along with occupying a pivotal position in the regulation of material and energy metabolism. Overt thyroid dysfunction is widely recognized to negatively affect female reproductive health.[8–10] Reduced ovarian reserve, menstrual abnormalities, and infertility may result from serious thyroid dysfunction due to direct and indirect interactions with the hypothalamic-pituitary-ovarian (HPO) axis and reproductive organs.[11] Compared with the control group, Goswami et al found that POI patients experienced significantly higher rates of clinical thyroid

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dysfunction.[12] A Mendelian randomization study found that genetically predicted celiac disease was associated with a 16% increased risk of POI, with hypothyroidism mediating 13.46% of this effect.[13] Subclinical hypothyroidism (SCH) may also impair female fertility, and there is a probability that it will progress to overt hypothyroidism.[14] A case-control study by Zhang et al reported decreased free triiodothyronine (FT_3), and free thyroxine (FT_4) levels alongside increased thyrotropin (TSH) in POI patients compared to controls.[15] Given the heterogeneous observations in the limited literature, the potential association between thyroid function and POI requires further clarification. Besides, some studies have shown a correlation between thyroid function and certain metabolic diseases.[16,17] Our previous research indicates that the prevalence of abnormal metabolism in glucose, lipids, and renal function may be higher among patients with POI compared to healthy controls.[18] Despite these findings, there is still a lack of clarity regarding the specific association between thyroid function and the metabolism of POI patients, which is an important area for future research.

Current limited literature suggests that thyroid function may differ between women with POI and controls, and that it may also be associated with certain metabolic markers. Therefore, we sought to compare thyroid function between women with POI and controls in this study. Additionally, we aimed to investigate the potential correlation between thyroid function and metabolic markers specifically in women with POI, which is a key innovative focus of this study.

Materials and Methods

Study Population and Data Collection

This cross-sectional case-control study recruited 227 women with POI aged 20–40 years out of 495 POI patients at the Women's Hospital, School of Medicine, Zhejiang University from January 2017 to January 2024 (The specific sample size estimation process is detailed in the Supplementary material). The criteria for a POI diagnosis included: (1) age under 40 years at initial diagnosis; (2) oligomenorrhea or amenorrhea lasting at least 4 months; and (3) elevated follicle-stimulating hormone (FSH) levels (>25 IU/L) on two separate occasions at least 4 weeks apart.[1] Patients with genetic or iatrogenic POI and primary amenorrhea were excluded. To increase the comparability of the study, we recruited 232 control women aged 20–40 years who visited the same hospital for benign gynecologic diseases (predominantly uterine fibroids or endometrial polyps) from January 2017 to January 2024. The control group had regular menstrual cycles and normal ovarian function, those with ovarian diseases or a history of ovarian surgery were not included.

In both the POI and control groups, women who matched any of the following criteria were excluded: overt thyroid diseases, thyroid tumor, history of thyroid surgery, and use of thyroid-related medications within 3 months; consumption of traditional Chinese medicine, or drugs that can significantly affect metabolism within 3 months; receipt of hormone therapy; endocrine diseases; severe systemic diseases; autoimmune diseases; pregnancy and lactation within 6 months; acute and chronic infectious diseases; history of malignant tumor; psychological disorders (The exclusion and inclusion process is detailed in the Supplementary Figure).

All patients underwent a standardized investigation at the first visit, which included detailed medical history, physical examination, anthropometric evaluation, transvaginal or transabdominal ultrasound, and laboratory tests. In-person interviews with qualified medical personnel were conducted to collect reproductive characteristics and menstrual history. All individuals' anthropometric information, such as height, weight, and other measurements, were recorded. Body mass index (BMI; kg/m^2) is calculated by dividing the weight (kg) by the square of the height (m^2). The study protocol was in accordance with the Declaration of Helsinki and received approval from the Human Ethics Committee of Women's Hospital, Zhejiang University School of Medicine (No. 20140006). Each participant provided written informed consent.

Thyroid Function, Sex Hormones, and Metabolic Assessment

Following an overnight fast, venous blood was collected from all patients the next morning during their initial visit. Serum sex hormone levels in the control group were measured during the early follicular phase of the menstrual cycle. All samples were collected and utilized in accordance with the manufacturer's instructions. Serum TSH, FT_3, and FT_4 were measured using Abbott Architect i4000/ISR52244/ISR53344 Automatic Chemiluminescence Analyzer (Abbott Diagnostics, Abbott Park, IL, USA). The laboratory reference range for TSH was 0.35–4.94 mIU/L, while for FT_3 and FT_4, the reference ranges were 2.43–6.01 pmol/L and 9.01–19.05 pmol/L, respectively. The diagnostic criteria of SCH

comprised a raised serum TSH level in conjunction with a normal FT_4 level. The serum levels of FSH, luteinizing hormone (LH), and 17β-estradiol (E2) were tested by electrochemiluminescent immunoassay using a Roche Cobas 8000 e602 Analyzer (Roche Diagnostics, Meylan, France). Serum concentrations of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, hypersensitive insulin, creatinine, urea, and uric acid were determined on Abbott Architect C16000/C1600757 Automatic Biochemical Analyzer (Abbott Diagnostics, Abbott Park, IL, USA).

Statistical Analysis

To assess normality for continuous variables, the Kolmogorov–Smirnov test was employed. Data are presented as the mean ± SD for normal distribution variables or the median (with interquartile ranges; IQR) for non-normal distribution variables. To evaluate differences between POI patients and controls, Student's *t*-test and Mann–Whitney *U*-test were applied to normally and non-normally distributed continuous variables. Categorical variables were presented as n (%), and group comparisons were performed using the Chi-square test. With age and BMI as covariates, unadjusted and adjusted binary logistic regression models were developed to investigate the correlation between POI status and thyroid function. Further Spearman and Pearson correlation analysis of thyroid function with sex hormones and metabolic markers was conducted in the POI group. To control for the confounding effect of BMI, partial correlation analysis was employed to assess the associations between thyroid hormones and metabolic markers. Finally, the sex hormones and metabolic markers were compared according to the grouping of TSH < 2.5mU/L and TSH ≥ 2.5mU/L. Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) with $P < 0.05$ considered statistically significant.

Results

General Characteristics and Thyroid Function of POI Patients

The mean age of POI patients was 35.26 ± 5.14 years with a mean amenorrhea age of 34.37 ± 5.33 years. The serum sex hormone levels in the POI group were FSH 72.12 ± 34.44 IU/L, LH 39.57 ± 17.11 IU/L, and E2 29.21 (18.35, 130.50) pmol/L. The comparison of thyroid function between women with POI and controls is presented in Table 1. Between POI patients and controls, no difference was found in their mean age (35.26 ± 5.14 years vs 34.75 ± 4.97 years, P = 0.288). The mean BMI of POI patients was significantly lower than controls (21.34 ± 2.42 kg/m^2 vs 21.95 ± 2.66 kg/m^2, P = 0.010). Compared with controls, the serum levels of FT_3 (4.43 ± 0.55 pmol/L vs 4.22 ± 0.48 pmol/L, P < 0.001), FT_4 (14.07 [12.93, 15.37] pmol/L vs 13.11 [12.31, 13.87] pmol/L, P < 0.001), and the proportion of TSH ≥ 2.5mIU/L (3.52% vs 1.72%, P = 0.043) were significantly higher in women with POI, with all values remaining within the normal reference range. Serum TSH levels and the SCH proportion between POI patients and controls did not differ significantly (P > 0.05 for both).

Table 1 Comparison of the Thyroid Function Between POI Patients and Controls

	POI (n = 227)	Controls (n = 232)	P-value
Age, y	35.26 ± 5.14	34.75 ± 4.97	0.288
BMI, kg/m^2	21.34 ± 2.42	21.95 ± 2.66	**0.010**
TSH, mIU/L	1.67 (1.22, 2.35)	1.51 (1.16, 2.07)	0.142
FT_3, pmol/L	4.43 ± 0.55	4.22 ± 0.48	**< 0.001**
FT_4, pmol/L	14.07 (12.93, 15.37)	13.11 (12.31, 13.87)	**< 0.001**
TSH ≥ 2.5mIU/L	51 (22.47%)	35 (15.09%)	**0.043**
SCH	8 (3.52%)	4 (1.72%)	0.205

Notes: P-value < 0.05 was considered statistically significant. Bold values indicate statistically significant P-values (P < 0.05).

Abbreviations: BMI, body mass index; TSH, thyroid stimulating hormone; FT_3, free triiodothyronine; FT_4, free thyroxine; SCH, subclinical hypothyroidism.

Association Between Thyroid Function and POI

Logistic regression analyses were conducted to assess the correlation between thyroid function and POI, as shown in Table 2. In the unadjusted model, the serum levels of FT_3 and FT_4 were found to have a positive correlation with the risk of POI. The correlation remained after age and BMI adjustments. However, there was no significant correlation between TSH and POI in either the unadjusted or adjusted models.

Correlation of Thyroid Hormones with Sex Hormones and Metabolic Markers in POI Patients

Additional correlation analyses were conducted to evaluate the association between thyroid hormones and sex hormones, along with metabolic markers. As shown in Table 3, serum levels of glucose (r = 0.176, P = 0.008) were positively associated with FT_3 levels in the POI group. Age exhibited a negative association with FT_3 levels (r = −0.195, P = 0.003). Moreover, women with POI who had increased FT_4 levels were found to have higher levels of FSH (r = 0.151, P = 0.023) and glucose (r = 0.171, P = 0.010).

Table 2 Association of Thyroid Function with POI in Binary Logistic Regression Analyses

	Unadjusted Model		**Adjusted Model**	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
TSH	1.139 (0.974, 1.330)	0.102	1.160 (0.991, 1.357)	0.065
FT_3	2.286 (1.567, 3.333)	**< 0.001**	2.459 (1.668, 3.623)	**< 0.001**
FT_4	1.561 (1.366, 1.784)	**< 0.001**	1.553 (1.357, 1.778)	**< 0.001**

Notes: Logistic regression analyses were unadjusted or adjusted for age and BMI, as compared with healthy controls. P-value < 0.05 was considered statistically significant. Bold values indicate statistically significant P-values (P < 0.05).
Abbreviations: TSH, thyroid stimulating hormone; FT_3, free triiodothyronine; FT_4, free thyroxine.

Table 3 Correlation of Thyroid Hormones with Sex Hormones and Metabolic Markers in POI Patients

	TSH		**FT_3**		**FT_4**	
	r	**P**	**r**	**P**	**r**	**P**
Age	0.010	0.886	**−0.195**	**0.003**	−0.057	0.394
BMI	0.026	0.695	0.078	0.239	−0.115	0.085
FSH	0.000	0.999	0.081	0.223	**0.151**	**0.023**
LH	0.034	0.609	0.107	0.107	0.053	0.429
FSH/LH	−0.007	0.915	−0.009	0.896	0.052	0.431
E2	0.035	0.599	−0.045	0.499	0.122	0.066
TG	0.024	0.150	0.034	0.606	−0.071	0.288
TC	0.055	0.409	−0.083	0.213	−0.046	0.489
HDL-C	−0.058	0.386	0.039	0.555	0.096	0.152
LDL-C	0.069	0.302	−0.074	0.270	−0.061	0.360
Uric acid	0.082	0.221	−0.041	0.544	0.091	0.172
Urea	−0.003	0.960	0.037	0.582	−0.034	0.616
Creatinine	−0.033	0.621	−0.030	0.655	0.023	0.730
Glucose	0.069	0.305	**0.176**	**0.008**	**0.171**	**0.010**
Hypersensitive insulin	0.047	0.482	0.030	0.658	−0.046	0.490

Notes: P-value < 0.05 was considered statistically significant. Bold values indicate statistically significant P-values (P < 0.05).
Abbreviations: TSH, thyroid stimulation hormone; FT_3, free triiodothyronine; FT_4, free thyroxine; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, 17β-estradiol; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 4 Comparison of Sex Hormones and Metabolic Markers in POI Patients with TSH ≥ 2.5 mIU/L and TSH < 2.5 mIU/L

	TSH ≥ 2.5 mIU/L	TSH < 2.5 mIU/L	P-value
n	51	176	
Age, y	38 (34, 40)	37 (33, 39)	0.089
BMI, k/m^2	20.95 (19.62, 22.58)	20.96 (20.40, 22.43)	0.524
FT_3, pmol/L	4.50 ± 0.55	4.42 ± 0.55	0.358
FT_4, pmol/L	13.52 (12.55, 15.18)	14.14 (12.96, 15.46)	0.171
FSH, IU/L	73.23 ± 32.42	71.80 ± 35.08	0.794
LH, IU/L	43.03 ± 16.48	38.57 ± 17.20	0.101
FSH/LH	1.70 (1.30, 2.33)	1.88 (1.52, 2.37)	0.229
E2, pmol/L	32.86 (18.35, 144.40)	28.55 (18.35, 125.40)	0.557
TG, mmol/L	0.95 (0.75, 1.52)	0.92 (0.71, 1.23)	0.261
TC, mmol/L	4.77 (4.28, 5.43)	4.68 (4.26, 5.18)	0.302
HDL-C, mmol/L	1.43 (1.24, 1.71)	1.52 (1.34, 1.76)	0.089
LDL-C, mmol/L	2.49 (2.07, 2.99)	2.41 (2.05, 2.73)	0.181
Glucose, mmol/L	5.18 (4.96, 5.47)	5.16 (4.97, 5.38)	0.698
Hypersensitive insulin, mU/L	6.30 (4.70, 8.25)	6.30 (5.09, 8.90)	0.326
Creatinine, μmol/L	73.80 (69.20, 79.50)	74.22 (70.03, 79.08)	0.895
Urea, μmol/L	4.33 (3.88, 5.18)	4.48 (3.92, 5.22)	0.693
Uric acid, μmol/L	273.59 ± 52.02	263.58 ± 52.91	0.234

Abbreviations: TSH, thyroid stimulation hormone; BMI, body mass index; FT_3, free triiodothyronine; FT_4, free thyroxine; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, 17 β-estradiol; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Comparison of Sex Hormones and Metabolic Markers in POI Patients with Different TSH Levels

No significant difference in sex hormones and metabolic markers was observed between the POI subgroups with TSH levels ≥ 2.5 mIU/L and < 2.5 mIU/L (Table 4).

Discussion

In this study, women with POI demonstrated higher levels of FT_3 and FT_4, accompanied by a higher proportion of TSH ≥ 2.5 mIU/L in comparison to the control group. Elevated serum levels of FT_3 and FT_4 was found to be associated with a higher risk of POI. Additionally, we observed a positive correlation between FT_3 and FT_4 concentrations and serum glucose levels among POI patients. However, there were no significant differences in sex hormone and metabolic markers between the POI subgroups with TSH levels ≥ 2.5 mIU/L and those with TSH levels < 2.5 mIU/L.

Thyroid hormones play a crucial role in regulating female reproductive health. TSH, FT_3, and FT_4 can bind to receptors on different ovarian cells and have an impact on follicular growth and ovarian function.[19–21] When compared to healthy women, women with premature ovarian failure showed a higher prevalence of thyroid dysfunction.[12] We discovered that POI patients had higher levels of FT_3 and FT_4 than controls, and that higher FT_3 and FT_4 were positively associated with POI, although the differences were clinically subtle and within normal ranges. Daan et al reported that women with POI exhibited increased serum FT_4 and comparable TSH levels compared to controls,[22] which was consistent with our results. However, in a Chinese case-control study designed to assess the correlation between serum perfluoroalkyl and polyfluoroalkyl substances and POI, patients with POI showed decreased levels of FT_3 and FT_4 and an increased level of TSH in comparison with controls.[15] Since the mean or median levels of TSH, FT_3, and FT_4 for both groups are within the normal reference range, whether this statistical association in our study holds clinical relevance requires further investigation through an expanded sample size in future studies. The impact of thyroid hormones on ovarian function is complex. It may be influenced by factors such as the level and duration of exposure and the presence of thyroid antibodies.[2,6,7,23,24] We also discovered that FT_4 was positively correlated with FSH. The mechanism might be

that thyroid hormones and FSH promote the proliferation of granulosa cells synergistically to compensate for impaired ovarian function.[21] However, there is relatively little research currently accessible on the subject of thyroid hormone and FSH interactions. Future studies could focus on whether the elevation of FSH has an effect on thyroid hormones.

The presence of SCH is frequently observed in individuals with ovarian dysfunction in clinical practice. SCH has a risk of progressing to overt hypothyroidism, especially in individuals with circulating thyroid peroxidase autoantibodies,[14] which are noticeable in women with POI. Based on our research, SCH was not significantly more common among women with POI compared to controls. Multiple studies have shown that SCH was related to a decreased ovarian reserve.[25,26] However, a large-scale cross-sectional study in Belgium indicated that there were no differences in the levels of FT_4 and TSH, as well as the occurrence of overt hypothyroidism or SCH, among women with low, normal, or high ovarian reserve,[27] and similar findings were reported by an Italian research team.[28] Owing to the limited sample of this study, further research is needed to determine whether SCH will have adverse effects on ovarian function and its underlying mechanisms.

TSH is a sensitive indicator for evaluating thyroid function. According to our research, more POI patients than controls had TSH levels ≥ 2.5 mIU/L, while further analyses failed to reveal any correlation between TSH and POI as well as sex hormones. The atypical thyroid hormone profile observed in our POI group—characterized by concurrent elevations in FT_3/FT_4 and TSH—suggests a dysregulation that warrants deeper mechanistic exploration. Ząbczyńska et al discovered that immunoassayed TSH levels may not fully reflect bioactivity, as alterations in TSH glycosylation patterns in autoimmune contexts might contribute to a dissociation from circulating thyroid hormone levels.[29] Reduced anti-Müllerian hormone (AMH) and Antral follicle count (AFC) levels were related to high-normal TSH levels (2.5–4.2 mIU/L), and these effects were particularly pronounced in women with ovulatory dysfunction and unexplained infertility.[28] Thyroid autoimmunity was associated with an increased risk of overt POI in euthyroid women with TSH > 2.5 mIU/L.[30] But a retrospective study reported that there were no differences in AMH, basal FSH, and AFC among the three groups with TSH < 2.5, 2.5–4.0, or ≥ 4.0 mIU/L.[31] For women in the early stages of pregnancy and those undergoing assisted reproductive technology, it is recommended to maintain serum TSH levels below 2.5 mIU/L.[32] Despite the findings of this study not supporting the utilization of TSH ≥ 2.5 mIU/L as a clinical intervention threshold in all POI patients, the low natural pregnancy rate among these individuals suggests a heightened necessity for assisted reproductive techniques. Consequently, clinical awareness of potential thyroid function variations and collaboration with endocrinologists for accurate diagnosis remain important. For POI patients who have no recent fertility needs and no overt thyroid dysfunction, it is also necessary to avoid potential adverse effects of overtreatment.

As a result of hypoestrogenemia, POI is recognized as a risk factor for metabolic abnormalities.[33] Since thyroid function and glucose metabolism are closely linked,[34] both hyperthyroidism and hypothyroidism may increase the risk of developing diabetes.[16] Our study additionally found that FT_3 and FT_4 were positively correlated with serum glucose levels in POI patients, although the correlation coefficients were weak. Some studies have shown that TSH was positively associated with hyperglycemia in euthyroid subjects,[35,36] but no significant correlation was found in another study.[37] Luna-Vazquez reported a positive relationship between FT_4 and hyperglycemia,[38] whereas Pergola et al provided an opposite opinion.[37] As with our findings, previous studies also demonstrated a positive relationship between FT_3 and hyperglycemia and insulin resistance.[38,39] In conclusion, the effects of thyroid hormones on metabolic metrics are enigmatic and complicated. Notably, the positive association in our study (Table 3) contrasts with the lack of significant metabolic differences when the POI group was dichotomized by a TSH ≥ 2.5 mIU/L threshold (Table 4). This discrepancy implies that the thyroid-metabolism link in POI is likely a continuous spectrum of minor covariation rather than a threshold-dependent effect, which may explain the inconsistent results in our study. Consequently, the clinical relevance of these observed associations appears limited at present, highlighting the need for future research to confirm and extend these preliminary findings.

There are several limitations to our study. First, our study refrained from a deeper examination of thyroid autoimmunity in POI patients owing to the absence of data. Second, detailed markers of ovarian reserve (such as AMH and AFC) were not available, limiting our ability to directly correlate thyroid function with quantitative ovarian reserve. Third, as a cross-sectional, single-center study, the results may be subject to selection bias and cannot establish causality or determine the temporal interaction between thyroid function and POI. Finally, although statistically significant, the

observed differences in thyroid hormones and their associations with metabolic markers were weak in magnitude. Future multi-center longitudinal studies incorporating autoimmune profiling, detailed ovarian reserve assessment, and repeated measurements are warranted to validate and extend our findings.

Conclusion

This study suggested that elevated thyroid hormone levels within normal ranges, despite subtle clinical differences, were positively associated with POI, and there was a weak positive correlation between thyroid hormones and blood glucose in the POI patients, while the biological and clinical relevance requires further determination. Future studies should incorporate more comprehensive data collection and dedicated mechanistic investigations to fully elucidate the complex interplay between thyroid function, POI, and metabolic markers.

Data Sharing Statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Ethics Approval Statement

This study was conducted according to the Declaration of Helsinki. The ethics committee of Women's Hospital, Zhejiang University School of Medicine has approved the study (No. 20140006). Informed consent was obtained from all individual participants included in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Webber L, Davies M, Anderson R, et al; European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod*. 2016;31(5):926–937. doi:10.1093/humrep/dew027
2. Stuenkel CA, Gompel A. Primary ovarian insufficiency. *N Engl J Med*. 2023;388(2):154–163. doi:10.1056/NEJMcp2116488
3. Ishizuka B. Current understanding of the etiology, symptomatology, and treatment options in Premature Ovarian Insufficiency (POI). *Front Endocrinol*. 2021;12:626924. doi:10.3389/fendo.2021.626924
4. Li M, Zhu Y, Wei J, Chen L, Chen S, Lai D. The global prevalence of premature ovarian insufficiency: a systematic review and meta-analysis. *Climacteric*. 2023;26(2):95–102. doi:10.1080/13697137.2022.2153033
5. McDonald IR, Welt CK, Dwyer AA. Health-related quality of life in women with primary ovarian insufficiency: a scoping review of the literature and implications for targeted interventions. *Hum Reprod*. 2022;37(12):2817–2830. doi:10.1093/humrep/deac200
6. Szeliga A, Calik-Ksepka A, Maciejewska-Jeske M, et al. Autoimmune diseases in patients with premature ovarian insufficiency—our current state of knowledge. *Int J Mol Sci*. 2021;22(5):2594. doi:10.3390/ijms22052594
7. Sharif K, Watad A, Bridgewood C, Kanduc D, Amital H, Shoenfeld Y. Insights into the autoimmune aspect of premature ovarian insufficiency. *Best Pract Res Clin Endocrinol Metab*. 2019;33(6):101323. doi:10.1016/j.beem.2019.101323

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. Weghofer A, Barad DH, Darmon S, Kushnir VA, Gleicher N. What affects functional ovarian reserve, thyroid function or thyroid autoimmunity? *Reprod Biol Endocrinol*. 2016;14(1):26. doi:10.1186/s12958-016-0162-0
10. Kuroda M, Kuroda K, Segawa T, et al. Levothyroxine supplementation improves serum anti-Müllerian hormone levels in infertile patients with Hashimoto's thyroiditis. *J Obstet Gynaecol Res*. 2018;44(4):739–746. doi:10.1111/jog.13554
11. Poppe K. Management of endocrine disease: thyroid and female infertility: more questions than answers?! *Eur J Endocrinol*. 2021;184(4):R123–R135. doi:10.1530/EJE-20-1284
12. Goswami R, Marwaha RK, Goswami D, et al. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type 1 diabetes and premature ovarian failure. *J Clin Endocrinol Metab*. 2006;91(11):4256–4259. doi:10.1210/jc.2006-1005
13. Hou Y, Song W, Wei G, et al. Genetic mediators of celiac disease and premature ovarian failure: hypothyroidism and systemic lupus erythematosus. *Am J Reprod Immunol*. 2025;93(2):e70038. doi:10.1111/aji.70038
14. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. *JAMA*. 2019;322(2):153. doi:10.1001/jama.2019.9052
15. Zhang S, Tan R, Pan R, et al. Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women. *J Clin Endocrinol Metab*. 2018;103(7):2543–2551. doi:10.1210/jc.2017-02783
16. Laclaustra M, Moreno-Franco B, Lou-Bonafonte JM, et al. Impaired sensitivity to thyroid hormones is associated with diabetes and metabolic syndrome. *Diabetes Care*. 2019;42(2):303–310. doi:10.2337/dc18-1410
17. Mehran L, Delbari N, Amouzegar A, Hasheminia M, Tohidi M, Azizi F. Reduced sensitivity to thyroid hormone is associated with diabetes and hypertension. *J Clin Endocrinol Metab*. 2022;107(1):167–176. doi:10.1210/clinem/dgab646
18. Huang Y, Lv Y, Qi T, et al. Metabolic profile of women with premature ovarian insufficiency compared with that of age-matched healthy controls. *Maturitas*. 2021;148:33–39. doi:10.1016/j.maturitas.2021.04.003
19. Dosiou C. Thyroid and Fertility: recent Advances. *Thyroid*. 2020;30(4):479–486. doi:10.1089/thy.2019.0382
20. Aghajanova L, Lindeberg M, Carlsson IB, et al. Receptors for thyroid-stimulating hormone and thyroid hormones in human ovarian tissue. *Reprod Biomed Online*. 2009;18(3):337–347. doi:10.1016/S1472-6483(10)60091-0
21. Vissenberg R, Manders VD, Mastenbroek S, et al. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. *Hum Reprod Update*. 2015;21(3):378–387. doi:10.1093/humupd/dmv004
22. Daan NMP, Muka T, Koster MPH, et al. Cardiovascular risk in women with premature ovarian insufficiency compared to premenopausal women at middle age. *J Clin Endocrinol Metab*. 2016;101(9):3306–3315. doi:10.1210/jc.2016-1141
23. Hsieh YT, Ho JYP. Thyroid autoimmunity is associated with higher risk of premature ovarian insufficiency—a nationwide Health Insurance Research Database study. *Hum Reprod*. 2021;36(6):1621–1629. doi:10.1093/humrep/deab025
24. Allshouse AA, Semple AL, Santoro NF. Evidence for prolonged and unique amenorrhea-related symptoms in women with premature ovarian failure/primary ovarian insufficiency. *Menopause*. 2015;22(2):166–174. doi:10.1097/GME.0000000000000286
25. Hasegawa Y, Kitahara Y, Osuka S, Tsukui Y, Kobayashi M, Iwase A. Effect of hypothyroidism and thyroid autoimmunity on the ovarian reserve: a systematic review and meta-analysis. *Reprod Med Biol*. 2021;21(1):e12427. doi:10.1002/rmb2.12427
26. Rao M, Wang H, Zhao S, et al. Subclinical hypothyroidism is associated with lower ovarian reserve in women aged 35 years or older. *Thyroid*. 2020;30(1):95–105. doi:10.1089/thy.2019.0031
27. Polyzos NP, Sakkas E, Vaiarelli A, Poppe K, Camus M, Tournaye H. Thyroid autoimmunity, hypothyroidism and ovarian reserve: a cross-sectional study of 5000 women based on age-specific AMH values. *Hum Reprod*. 2015;30(7):1690–1696. doi:10.1093/humrep/dev089
28. Giusti M, Mittica M. Evaluation of anti-Müllerian hormone in pre-menopausal women stratified according to thyroid function, autoimmunity and age. *Thyroid Res*. 2022;15(1):1–9. doi:10.1186/s13044-022-00133-5
29. Ząbczyńska M, Kozłowska K, Pocheć E. Glycosylation in the thyroid gland: vital aspects of glycoprotein function in thyrocyte physiology and thyroid disorders. *Int J Mol Sci*. 2018;19(9):2792. doi:10.3390/ijms19092792
30. Li Z, Xu S, Luo W, et al. Association between thyroid autoimmunity and the decline of ovarian reserve in euthyroid women. *Reprod Biomed Online*. 2022;45(3):615–622. doi:10.1016/j.rbmo.2022.05.015
31. Wu J, Zhao Y, Wang M, Tang M, Liu Y. Correlation analysis between ovarian reserve and thyroid hormone levels in infertile women of reproductive age. *Front Endocrinol*. 2021;12:745199. doi:10.3389/fendo.2021.745199
32. Alexander EK, Pearce EN, Brent GA, 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
33. Kunicki M, Kruszewska J, Skórska J, Laudy-Wiaderny H, Wrona M, Smolarczyk R. Does the value of FSH predict severity of metabolic complications in females with POI? *J Clin Med*. 2022;11(7):2024. doi:10.3390/jcm11072024
34. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocr Rev*. 2019;40(3):789–824. doi:10.1210/er.2018-00163
35. Park SB, Choi HC, Joo NS. The relation of thyroid function to components of the metabolic syndrome in Korean men and women. *J Korean Med Sci*. 2011;26(4):540–545. doi:10.3346/jkms.2011.26.4.540
36. Jun JE, Jee JH, Bae JC, et al. Association between changes in thyroid hormones and incident type 2 diabetes: a seven-year longitudinal study. *Thyroid*. 2017;27(1):29–38. doi:10.1089/thy.2016.0171
37. Bakiner O, Bozkirli E, Cavlak G, Ozsahin K, Ertorer E. Are plasma thyroid-stimulating hormone levels associated with degree of obesity and metabolic syndrome in euthyroid obese patients? A Turkish Cohort Study. *Int Sch Res Notices*. 2014;2014:e803028. doi:10.1155/2014/803028
38. Luna-Vazquez F, Cruz-Lumbreras R, Rodríguez-Castelán J, et al. Association between the serum concentration of triiodothyronine with components of metabolic syndrome, cardiovascular risk, and diet in euthyroid post-menopausal women without and with metabolic syndrome. *SpringerPlus*. 2014;3(1):1–8. doi:10.1186/2193-1801-3-266
39. De Pergola G, Ciampolillo A, Alò D, Sciaraffia M, Guida P. Free triiodothyronine is associated with smoking habit, independently of obesity, body fat distribution, insulin, and metabolic parameters. *J Endocrinol Invest*. 2010;33(11):815–818. doi:10.1007/BF03350348