BMC Endocrine Disorders

RESEARCH

Open Access

The relationship between serum CTRP-5, C3a/desArg, and complement-C3 levels and hypothyroidism in women with polycystic ovary syndrome

Fatima Abdul-ameer[1,2], Itlal Jummha AbudlRasool AlAsadi[2], Asieh Hosseini[3] and Elham Bahreini[1*]

Abstract

Introduction Many patients with polycystic ovary syndrome (PCOS) also experience thyroid disorders. There is a notable similarity in energy metabolism among PCOS, C1q/tumor necrosis factor (TNF)-related proteins (CTRP-5) deficiency, C3a/desArg (also known as acylation-stimulating protein (ASP)) deficiency, and hypothyroidism. This study aimed to investigate the relationship between serum levels of these factors and hypothyroidism in patients with PCOS. Improved clarity and vocabulary, corrected minor grammatical issues, and enhanced readability.

Methods This case-control study involved three groups: healthy women (control group), women with PCOS and hypothyroidism, and women with PCOS without hypothyroidism. Serum levels of FBS, total cholesterol, triglycerides, and HDL-C were measured using enzymatic and colorimetric methods. TSH, T4, T3, and anti-thyroid peroxidase (Anti-TPO) levels were determined by ELISA to screen for hypothyroidism in women with PCOS. Additionally, serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), CTRP-5, ASP, and complement C3 were assessed using the ELISA method.

Results The results indicated that reduced blood levels of CTRP-5, along with elevated levels of ASP (C3a/desArg) and complement C3 in patients with PCOS, may be linked to dysregulation of the thyroid gland. Furthermore, the study observed that changes in these parameters, in conjunction with thyroid dysfunction, are associated with pathological alterations in lipid profiles and blood glucose levels.

Conclusion While changes in CTRP-5, ASP, and complement C3 can influence energy expenditure and storage in PCOS and thyroid function, the complex nature of PCOS requires further research to investigate the prevalence of hypothyroidism in individuals with PCOS.

Clinical trial number Not applicable

Keywords Polycystic ovary syndrome, Hypothyroidism, Complement C3, Adipokines

*Correspondence:
Elham Bahreini
Bahreini.e@iums.ac.ir; elhambahreini@yahoo.com
[1]Department of Biochemistry, Faculty of Medicine, Iran University of Medical Sciences, P.O. Box: 1449614525, Tehran, Iran
[2]College of Medicine, University of Karbala, Karbala, Iraq
[3]Razi Drug Research Center, Iran University of Medical Sciences, Tehran, Iran

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that commonly presents during reproductive years and significantly impacts fertility due to irregular menstrual cycles and anovulation. It can adversely affect oocyte quality, leading to increased rates of maturation defects and lower fertilization rates [1]. Additionally, PCOS is associated with endometrial dysfunction; a thickened endometrium can hinder implantation and elevate the risk of miscarriage, with elevated androgen levels that compromise endometrial receptivity [2, 3]. Women with PCOS also face a heightened risk of pregnancy complications such as gestational diabetes, preeclampsia, and preterm birth, primarily due to underlying metabolic issues [1, 2]. Therefore, Understanding the complex relationship between PCOS and these systemic disorders is crucial for effective management.

Women with PCOS are at a higher risk of developing thyroid disorders, particularly hypothyroidism, compared to women without PCOS [4, 5]. However, a common genetic background has not yet been established. Thyroid issues can exacerbate symptoms such as menstrual irregularities and metabolic disturbances, complicating the diagnostic process for PCOS [6]. Therefore, women with both thyroid disorders and PCOS may experience more severe symptoms of both conditions [4, 7].

Both PCOS and hypothyroidism disrupt hormonal balance and share overlapping symptoms, including irregular menstrual cycles [4, 8], weight gain, anxiety, fatigue, hair thinning, and mood swings [4, 9]. On the other hand, while hypothyroidism typically leads to dry skin and brittle nails, PCOS may cause acne and oily skin [10, 11]. Additionally, both conditions are associated with insulin resistance, increasing the risk of type 2 diabetes [12]. It is important to note that not all individuals with PCOS or hypothyroidism will exhibit all symptoms, and their severity can vary; thus, proper diagnosis and management by healthcare professionals are crucial to address individual needs.

Changes in adipokine levels have been observed in both PCOS and hypothyroidism, contributing to the metabolic disturbances associated with these conditions [13, 14]. For instance, adiponectin is an adipokine that enhances insulin sensitivity and possesses anti-inflammatory properties. The commonality between PCOS and hypothyroidism lies in the potential disruption of adiponectin signaling, which can lead to metabolic disturbances and insulin resistance in both conditions [14, 15]. CTRPs are another group of adipokines that share structural homology with adiponectin, including a collagen-like domain and a C1q-like globular domain. This structural similarity suggests that they may have overlapping functions in regulating metabolic pathways [16].

Complement 3 (or C3), a protein synthesized in the liver, plays a crucial role in the immune system and inflammation. Although direct research on the relationship between PCOS and C3 is limited, potential connections can be inferred based on their respective roles in metabolism and inflammation [17, 18]. Both PCOS and C3 are associated with chronic low-grade inflammation and increased cardiovascular risk factors, such as hypertension, dyslipidemia, and atherosclerosis [19]. Additionally, C3 is implicated in the development of insulin resistance and metabolic disorders. In response to various stimuli, including inflammatory and metabolic signals, C3 is cleaved by enzymes known as convertases into multiple bioactive fragments, one of which is Acylation Stimulating Protein (ASP) [18, 19]. ASP is primarily produced in adipose tissue through the cleavage of C3 and is closely related to C3 in terms of their interactions and biological functions. As a circulating hormone, ASP is primarily synthesized in adipose tissue and plays a significant role in regulating triglyceride synthesis and storage. Furthermore, ASP is known to interact with C3 and is involved in various metabolic processes, including insulin sensitivity, lipid metabolism, and energy balance [20, 21].

In hypothyroidism, there is evidence of alterations in C3 levels and ASP activity that may be linked to the metabolic disturbances observed in affected individuals. Some studies have reported elevated levels of C3 and a subsequent increase in ASP activity among those with hypothyroidism. The relationship between C3 and ASP in this condition suggests that variations in these components may be associated with metabolic complications, including abnormalities in lipid metabolism, storage, and energy balance. Similar to CTRPs, changes in C3 and ASP levels in both PCOS and hypothyroidism may indicate a complex interaction between these two disorders [22, 23].

While PCOS and hypothyroidism have distinct etiologies and clinical presentations, they may influence levels of CTRPs, C3, and ASP similarly. No prior studies have compared the blood levels of these factors in women with PCOS, both with and without hypothyroidism. Therefore, this research aims to investigate the differences in these levels between individuals with PCOS who have hypothyroidism and those who do not.

Materials and methods

Study population

This study was conducted on 100 women over the age of 18 who were diagnosed with PCOS by Dr. Alasadi. The selection of participants with PCOS was based on the Rotterdam criteria [24], which require the presence of at least two out of three items: hyperandrogenism (either clinical and/or biochemical), PCOS morphology as

assessed by ultrasound, and ovulatory dysfunction (manifested as irregular menstrual cycles). Pregnant women and those with systemic diseases, including kidney, liver, heart, and other systemic disorders, were excluded from the study. Since a high BMI makes individuals susceptible to metabolic diseases, including insulin resistance, reduced resting metabolic rate, impaired regulation of fatty acid oxidation, and dyslipidemia, as well as changes in adipokines such as leptin, adiponectin, and resistin, the entry of women who appear healthy but have a high BMI into the healthy group was prevented. However, due to the inevitable impact of PCOS on metabolism, screening in this regard was not conducted in patients with PCOS. Additionally, conditions that present with PCOS-like symptoms, such as hyperprolactinemia, Cushing's syndrome, non-classical adrenal hyperplasia, adrenal tumors, androgen-secreting tumors, idiopathic hirsutism, and idiopathic hyperplasia, were also considered exclusion criteria. The Ethics Commission of Iran University of Medical Sciences reviewed the project for compliance with the "Helsinki Declaration and approved the study (Ethical Code: IR.IUMS.REC.1402.669). After the doctor explained the project and ensured the confidentiality of personal data, all participants provided informed written consent to participate.

During the screening process, patients were divided into two groups of 50: those with hypothyroidism and those without. Additionally, a healthy control group of 50 women aged 18 to 45 years was selected from individuals visiting the clinic for check-ups, adhering to the same exclusion criteria.

Sampling

To minimize the effects of regulatory hormones, participants were in the early follicular phase of their menstrual cycle (around days of 1 to 4 of the cycle). The demographic information, including age, weight, and height, was directly collected from the participants. Blood samples were collected from participants after a 12-hour fasting period. After centrifugation at 4,000 rpm for 10 min, serum samples were extracted from whole blood and preserved at -80 °C until further testing.

Biochemical tests

The biochemical tests performed in this study were classified into three categories:

- **General tests**: FBS, TG, CHOL, HDL, and BMI.

Serum levels of fasting blood sugar [(FBG); GLUCOSE kit, range 5 to 400 mg/dl; sensitivity: 5 mg/dl], and lipid profile, including triglycerides [(TG); TRIGLYCERIDES kit, range 5 to 700 mg/dl; sensitivity: 5 mg/dl], total cholesterol [(CHOL); CHOLESTEROL kit, range 5 to 500 mg/dl; sensitivity: 5 mg/dl] high density lipoprotein [(HDL), HDL kit, range 1 to 150 mg/dl; sensitivity: 1 mg/dl] using the PARS AZMUN diagnostic kits (Tehran, Iran), according to the manufacturer's instructions by the Perestig24i auto-analyzer. LDL- cholesterol was calculated the *Friedewald* equation [LDL-C = Total CHOL - (HDL) - (TG/5)] [25]. Body mass index (BMI) was estimated as "body mass (kg)/ [height (m)]^2".

- **The screening tests for PCOS with / without thyroid desease**: T3, T4, TSH, and Anti-TPO.

The thyroid profile, which includes T3, T4, TSH, and Anti-TPO assays, was analyzed using the Competitive Enzyme Immunoassay method in accordance with the manufacturer's instructions.

- **Specialized tests**: complement C3, FSH, LH, CTRP-5 and ASP.

Specialized tests: complement C3, FSH, LH, CTRP-5, and ASP. Complement C3, FSH, LH, CTRP-5, and ASP factors were assessed using ELIZA method, following the manufacturer's instructions.

Statistical analysis

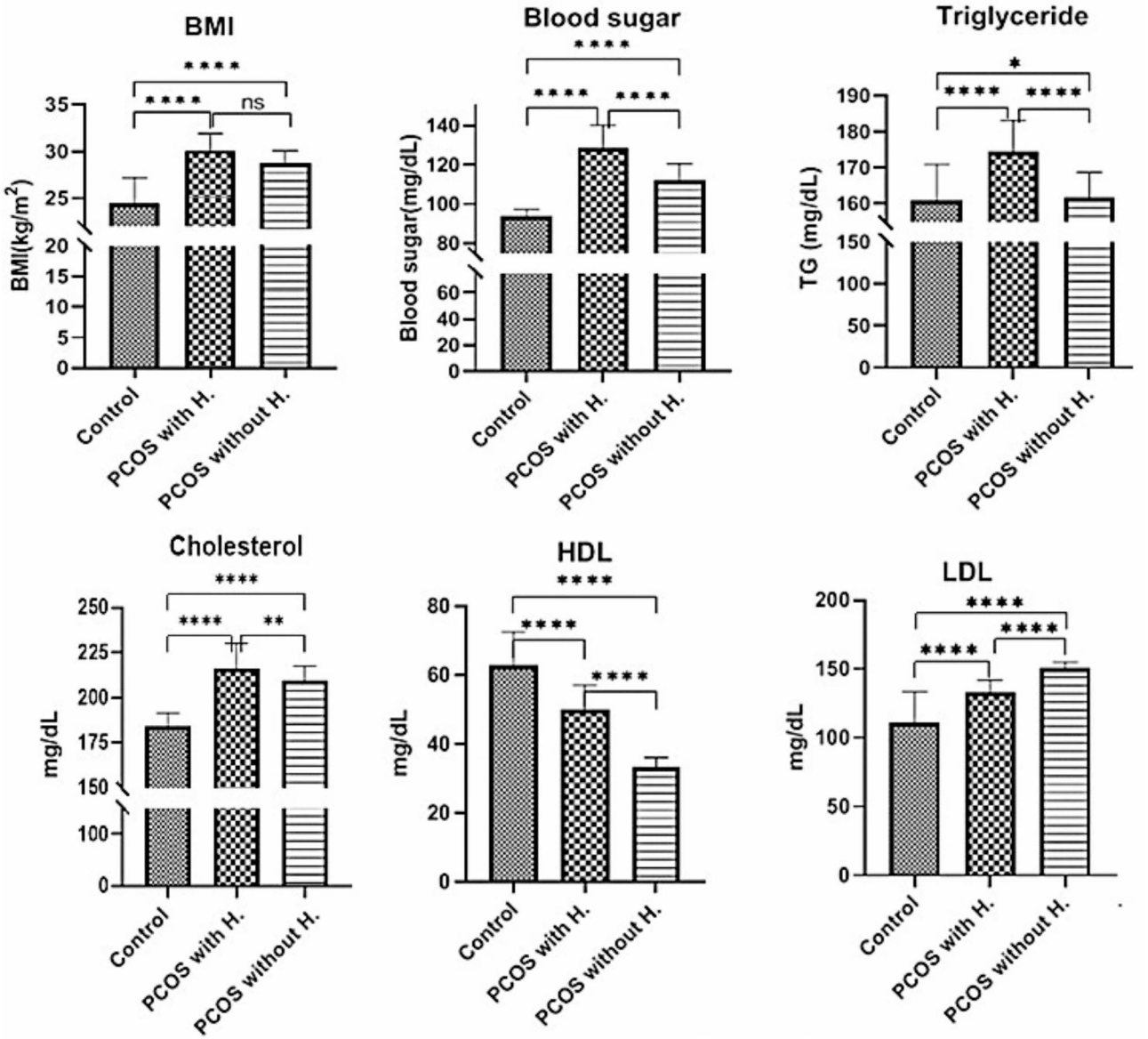
Statistical analysis was performed using SPSS software version 22 and GraphPad Prism 9. The normality of the data was confirmed through the Shapiro-Wilk normality test. Variances among groups were assessed using one-way ANOVA, followed by Tukey's test for post-hoc pairwise comparisons. Results are presented as means ± standard deviation (SD), with statistical significance defined as a P-value < 0.05.

Results

The study groups of PCOS with hypothyroidism, PCOS without hypothyroidism and healthy control were matched in age, 40.24 ± 5.90, 38.58 ± 7.99, and 38.74 ± 7.66, respectively, P > 0.05.

Biochemical parameters

Figure 1 illustrates the BMI and levels of FBS, Triglyceride, cholesterol, HDL, LDL in the PCOS groups with and without hypothyroidism, and compares these with the healthy control group. A one-way ANOVA revealed significant differences in BMI and biochemical parameters among the study groups ($P < 0.0001$). Pairwise comparisons using Tukey's test indicated significantly higher BMI, blood sugar, cholesterol, and triglyceride levels ($P < 0.05$), as well as significantly lower HDL levels ($P < 0.05$) in PCOS patients compared to the healthy control group. Although cholesterol and triglyceride levels were elevated in PCOS patients with hypothyroidism, their HDL



	Intra-observed Coefficient of Variation (%)		
Test	**Control**	**PCOS with H.**	**PCOS without H.**
BMI	**3.82%**	**6.38%**	**3.96%**
BS	**4.17%**	**13.01%**	**7.78%**
TG	**6.28%**	**5.07%**	**4.47%**
Ch	**3.82%**	**6.38%**	**3.96%**
HDL	**15.22%**	**14.05%**	**8.29%**
LDL	**20.06%**	**5.98%**	**2.95%**

Fig. 1 Comparison of BMI (body mass index), FBS (fasting blood sugar), Triglyceride, cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein) levels among the study groups. Intra-observed Coefficient of Variation indicates how much variation there is in repeated measurements *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.001$

levels were significantly higher ($P<0.05$), LDL levels were significantly lower ($P<0.05$), and BMI was comparable to that of PCOS patients without hypothyroidism.

Thyroid test profiles

Figure 2 shows the levels of T3, T4, TSH, and Anti-TPO in the PCOS groups, both with and without hypothyroidism, and compares these levels to those of the healthy control group. A one-way ANOVA revealed significant differences in T3, T4, TSH, and Anti-TPO among the study groups ($P<0.0001$). Although the levels of T4, T3, TSH, and Anti-TPO in PCOS patients without hypothyroidism fell within the normal range as specified in the kit brochures—except for Anti-TPO—significant differences were noted in these hormones when comparing this group to the healthy control group. Pairwise comparisons using Tukey's test indicated that PCOS patients with hypothyroidism had significantly higher blood levels of TSH and Anti-TPO compared to those without hypothyroidism, while their blood levels of T4 and T3 were significantly lower ($P<0.05$).

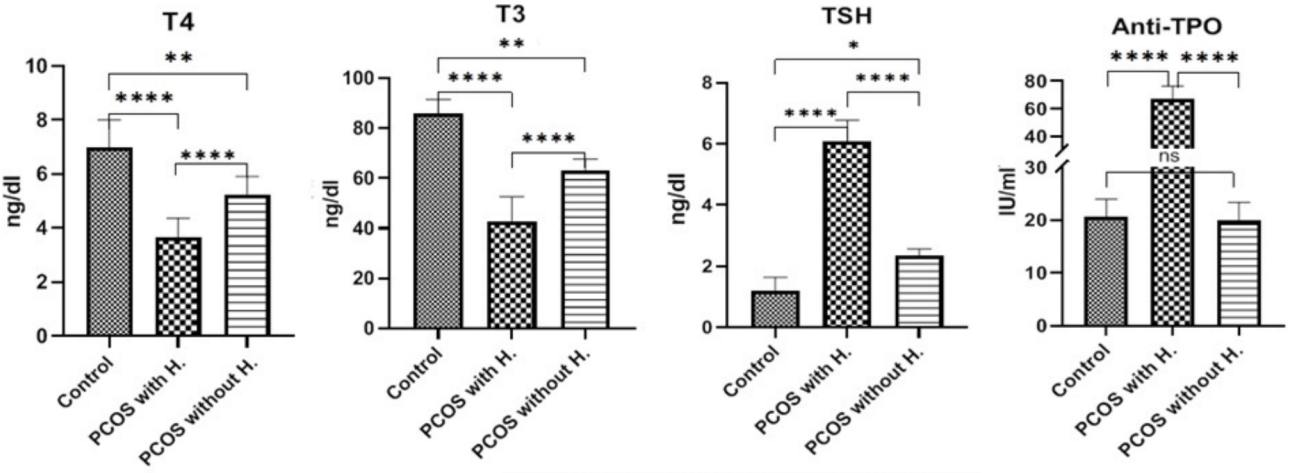
PCOS specialized tests

Figure 3 illustrates the blood levels of complement C3, FSH, LH, CTRP-5, and ASP in the PCOS groups, both with and without hypothyroidism, and compares these levels to those of the healthy control group. A one-way ANOVA revealed significant differences in complement C3, FSH, LH, CTRP-5, and ASP among the study groups ($P<0.0001$).

Pairwise comparisons of groups using Tukey's test revealed normal LH levels, but lower FSH levels in PCOS patients without hypothyroidism compared to the control group. Hypothyroidism in PCOS patients ($P<0.05$) compared to healthy controls; however, the blood levels of these factors were significantly lower in PCOS patients with hypothyroidism than in those without hypothyroidism ($P<0.05$).

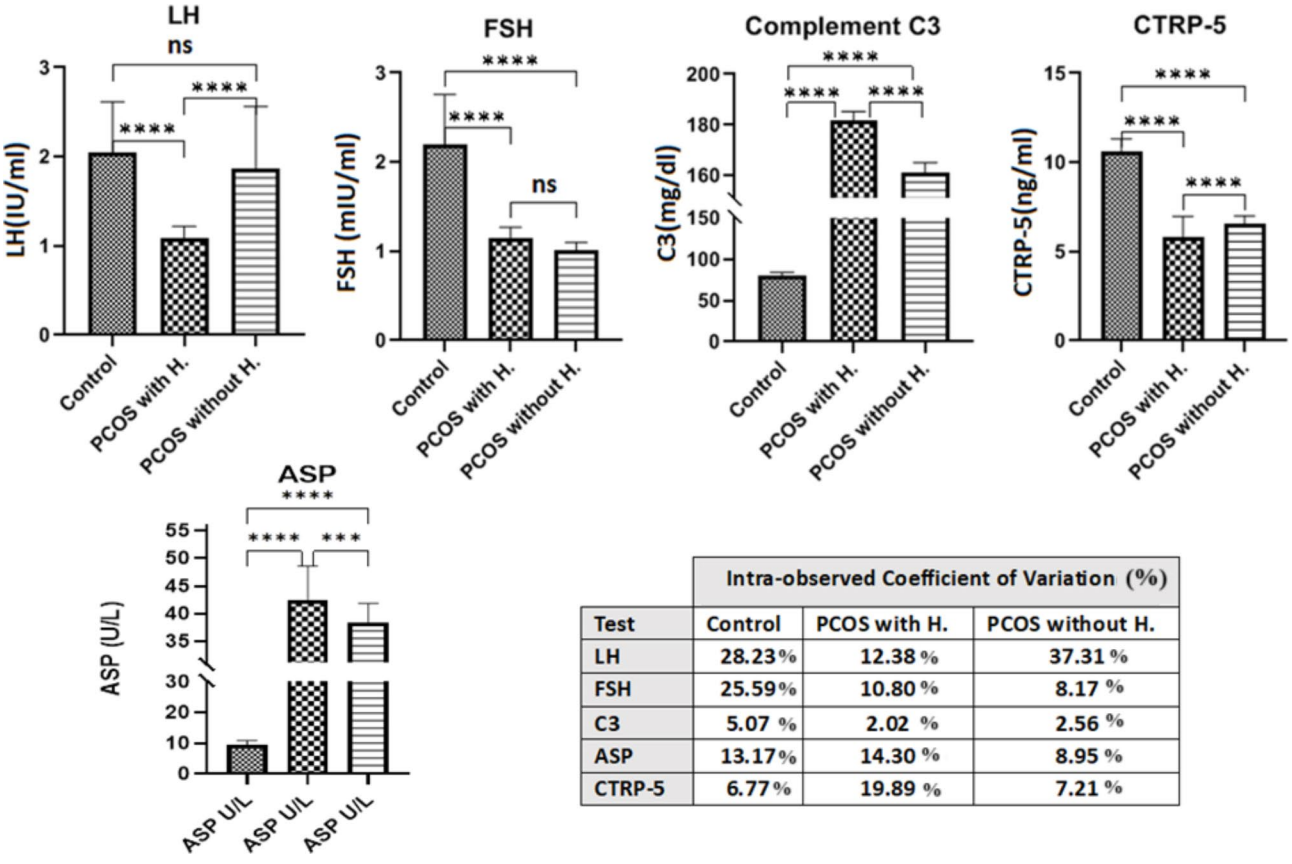
Correlations

Spearman correlations were calculated between CTRP-5, ASP, complement-C3, and Anti-TPO factors with metabolic parameters, including FBS, Triglycerides, Cholesterol, HDL, LDL, and BMI. With the exception of HDL, positive correlations were identified between CTRP-5, ASP, complement-C3, and Anti-TPO with BMI and the aforementioned metabolic parameters. However, these correlations were negative concerning CTRP-5 (Table 1). A positive association was noted between complement-C3 and ASP, while both parameters exhibited a negative association with CTRP-5 (Table 2). Additionally, complement-C3 and ASP demonstrated a negative correlation with thyroid hormones (T4 and T3) and a positive association with thyroid-stimulating hormone (TSH) and Anti-TPO, whereas CTRP-5 displayed the opposite effects (Table 3).



	Intra-observed Coefficient of Variation		
Test	Control	PCOS with H.	PCOS without H.
TSH	35.40%	11.44 %	8.81 %
T4	14.88 %	18.97 %	16.50 %
T3	6.47 %	22.37 %	7.48 %
Anti-TPO	15.95 %	13.39 %	17.76 %

Fig. 2 Comparison of T4, T3, TSH (thyroid-stimulating hormone), and Anti-TPO (anti–thyroid peroxidase) levels among the study groups. Intra-observed Coefficient of Variation indicates how much variation there is in repeated measurements. *: $P<0.05$, **: $P<0.01$, ***: $P<0.001$, ****: $P<0.001$



	Intra-observed Coefficient of Variation (%)		
Test	**Control**	**PCOS with H.**	**PCOS without H.**
LH	**28.23%**	**12.38%**	**37.31%**
FSH	**25.59%**	**10.80%**	**8.17%**
C3	**5.07%**	**2.02%**	**2.56%**
ASP	**13.17%**	**14.30%**	**8.95%**
CTRP-5	**6.77%**	**19.89%**	**7.21%**

Fig. 3 Comparison of FSH, LH, complement-C3, ASP (acylation-stimulating protein) and CTRP-5 (C1q/TNF-related protein 5) levels among the study groups. Intra-observed Coefficient of Variation indicates how much variation there is in repeated measurements. *: $P<0.05$, **: $P<0.01$, ***: $P<0.001$, ****: $P<0.001$

Table 1 Spearman correlation between CTRP-5, Complement-C3, ASP and Anti-TPO with metabolic parameters

Variables/ Correlation "*r*"	CTRP-5[1]	ASP[2]	Complement-C3	Anti-TPO[3]
BMI	-0.400**	0.540**	0.304**	0.083
FBS	-0.591**	0.735**	0.780**	0.485**
Triglyceride	-0.394**	0.328**	0.286**	0.412**
Cholesterol	-0.672**	0.617**	0.650**	0.327**
HDL	0.539**	-0.468**	-0.420**	0.277**
LDL	-0.849**	0.710**	0.678**	0.519**

**. Correlation is significant at the $P=0.01$ level

[1]: C1q/TNF-related protein 5; [2]: acylation-stimulating protein; [3]: anti–thyroid peroxidase

Table 2 Spearman correlation between CTRP-5, Complement-C3 and ASP with each other

Variables/ Correlation "*r*"	Complement-C3	CTRP-5[1]	ASP[2]
Complement-C3	1.000		
CTRP-5	-0.642**	1.000	
ASP	0.654**	-0.658**	1.000

**. Correlation is significant at the $P=0.01$ level

[1]: C1q/TNF-related protein 5; [2]: acylation-stimulating protein

Table 3 Spearman correlation between CTRP-5, Complement-C3 and ASP with thyroid parameters

Variables/ Correlation "*r*"	CTRP-5[1]	ASP[2]	Complement-C3
T3	0.794**	-0.762**	-0.706**
T4	0.629**	-0.650**	-0.708**
TSH[3]	-0.678**	0.749**	0.791**
Anti-TPO[4]	-0.296**	0.366**	0.438**

**. Correlation is significant at the $P=0.01$ level

[1]: C1q/TNF-related protein 5; [2]: acylation-stimulating protein; [3] thyroid-stimulating hormone; [4] anti–thyroid peroxidase

ROC curves of CTRP-5, ASP, and Complement-C3

The receiver operating characteristic (ROC) curve was analyzed to evaluate the diagnostic potential of CTRP-5, ASP, and complement C3 levels in differentiating individuals diagnosed with PCOS from healthy controls. The identified cutoffs for each biomarker represent optimal points that balance sensitivity and specificity for this diagnostic endpoint. The curves are skewed away from the 45° diagonal, with the curve for complement C3 shifted further up and to the left compared to those for ASP and CTRP-5. The cutoffs that provide the best balance between sensitivity and specificity, as determined by the intersection of the curves with the 100%-to-100%

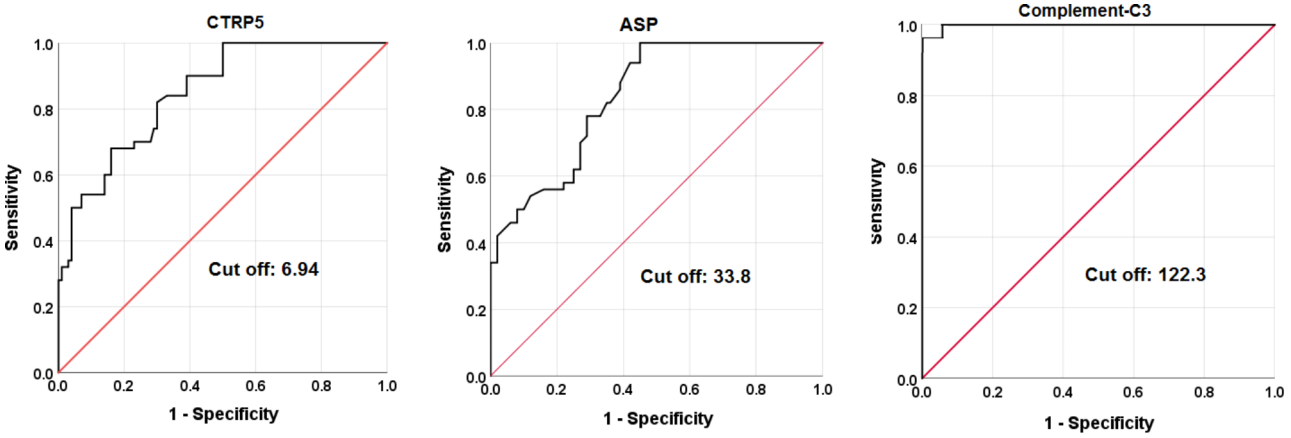
diagonal, are approximately 6.94 ng/ml for CTRP-5, 33.8 U/l for ASP, and 122.3 mg/dl for complement C3. As shown in Fig. 4, the area under the curve (AUC) for all three factors was significantly greater than 0.5 ($P<0.001$).

Discussions

The present study investigated the relationship between serum levels of CTRP-5, complement C3, and ASP in patients with hypothyroidism and PCOS. Previous research has demonstrated that these factors are altered in both hypothyroidism and PCOS [26–29], However, no studies have been found that specifically examine the relationship between these factors and hypothyroidism in patients with PCOS.

The case-control groups matched for age but not for BMI. PCOS is known to affect metabolism, often resulting in an increase in BMI, particularly when it coexists with hypothyroidism, which further slows metabolic rates. However, despite the differences in BMI between healthy controls and individuals with PCOS, our study found no significant difference in BMI between the two groups of PCOS women—those with and without hypothyroidism. Consistent with previous studies [30, 31], this study also demonstrated that PCOS is associated with decreased blood levels of CTRP-5. Furthermore, a more pronounced decrease in blood CTRP-5 levels was observed in women with PCOS and hypothyroidism compared to those with PCOS alone. One of the most common symptoms associated with PCOS is being overweight or experiencing difficulty losing weight due to insulin resistance. Generally, CTRP-5 is negatively correlated with insulin resistance, the free androgen index, and BMI. Several studies, including one conducted by Jiang et al., have reported an association between CTRP-5 and the regulation of glucose and lipid metabolism [32–34]. They demonstrated a negative correlation between this factor and the increased risk of metabolic syndrome, linking it to the development of insulin resistance [35]. Therefore, the increase in BMI, blood sugar levels, and lipid profiles in patients with PCOS is likely related to a decrease in CTRP-5 and, to some extent, an increase in insulin resistance. Additionally, the positive relationship between thyroid hormones and catabolism helps explain the rise in these parameters among PCOS patients with hypothyroidism. The structural similarities between CTRP-5 and adiponectin provide insight into the relationship between CTRP-5 and metabolic disorders, such as obesity. Consequently, similar to adiponectin, decreased levels of CTRP-5 contribute to the development of metabolic disturbances [36–40] .

Complement pathway proteins, particularly complement C3, are elevated in individuals with PCOS and can be influenced by factors such as obesity and insulin resistance. The activation of C3 results in the formation of C3a, which subsequently converts to C3adesArg, also known as ASP. ASP interacts with adipocytes through its receptor C5L2, promoting triglyceride synthesis and enhancing lipid storage. Research indicates that ASP levels are significantly elevated in PCOS, particularly in patients with concurrent hypothyroidism, which further intensifies ASP levels [41–43]. The presence of high C3 and ASP levels in non-hypothyroid PCOS patients may



Area Under the Curve		
Test Results Variable(s): CTRP5		
Area	Std. Errora	Asymptotic Sig.b
0.849	0.031	0.00

Area Under the Curve		
Test Results Variable(s): ASP		
Area	Std. Errora	Asymptotic Sig.b
0.84	0.032	0.00

Area Under the Curve		
Test Results Variable(s): complement-C3		
Area	Std. Errora	Asymptotic Sig.b
0.998	0.002	0.00

Fig. 4 ROC (receiver operating characteristic) curves for CTRP-5 (C1q/TNF-related protein 5), ASP (anti–thyroid peroxidase), and complement-C3 in evaluating subjects with PCOS

account for similar triglyceride levels despite variations in BMI. In hypothyroid PCOS patients, reduced metabolism due to lower thyroid hormone levels may contribute to increased triglyceride levels. Additionally, the heightened presence of C3 receptors in hepatocytes in PCOS may lead to elevated triglycerides, cholesterol, and LDL levels, potentially increasing VLDL production and its release into the bloodstream. Cakir and Simsek [44] also found that total cholesterol/HDL (TC/HDL), triglycerides/HDL (TG/HDL) and LDL/HDL levels were significantly higher in patients with PCOS than in control group. Hypothyroidism is associated with increased BMI, blood triglycerides, cholesterol and LDL levels [45, 46]. Alterations in lipid and glucose metabolism can influence adipokine hormone levels. Several studies have explored the relationship between thyroid hormones and adipokines [38, 47, 48], however, there is no direct evidence regarding how thyroid hormones affect the synthesis and secretion of CTRP-5, ASP, or C3. Haiying et al. reported that hypothyroidism is associated with increased ASP levels and decreased adiponectin levels [49]. However, no research has been conducted on the relationship between CTRP-5 and hyperthyroidism or hypothyroidism. The majority of women with PCOS are likely to develop hypothyroidism [45]. According to Sethi [50], this may result from a dysfunction in the hypothalamic-pituitary-ovarian axis, leading to insufficient thyroid hormone production. Padalkar et al. [51] suggested that metabolic disorders in women with PCOS might be associated with the presence of unopposed estrogen, which is known to trigger autoimmune reactions, such as the production of thyroid peroxidase antibodies.

PCOS and hypothyroidism share several symptoms, including fatigue, weight gain, depression, and menstrual irregularities, which can lead to potential misdiagnosis, particularly in middle-aged women. Both conditions affect fertility and the reproductive cycle. Low levels of thyroid hormones can disrupt ovulation, cause luteal phase defects, and alter the balance of sex hormones, potentially resulting in polycystic ovaries that resemble those seen in PCOS. While changes in energy utilization and storage in PCOS can impact thyroid function, the primary finding of this research was the elevated levels of Anti-TPO antibodies in individuals with both hypothyroidism and PCOS, similar to those observed in Hashimoto's hypothyroidism [52, 53]. However, the connection between these conditions has yet to be fully understood. In Hashimoto's thyroiditis, the immune system gradually targets and inflames the cells in the thyroid gland over an extended period, resulting in chronic inflammation. Conversely, most individuals with PCOS exhibit elevated levels of chronic inflammation. Both chronic inflammation and PCOS are associated with several potential complications, including type 2 diabetes, obesity, and possibly thyroid disorders. Hypothyroidism not only exacerbates the symptoms of PCOS—such as weight gain, irregular menstrual cycles, and increased insulin resistance—but it can also lead to symptoms that are not typically associated with PCOS. These symptoms may include goiters (enlarged thyroid glands), facial rounding (moon facies), and bradycardia (abnormally slow heart rate).

Conclusions

In conclusion, our study highlights distinct metabolic and hormonal differences between PCOS patients with and without hypothyroidism. While both groups exhibited significantly higher BMI, blood glucose, cholesterol, and triglyceride levels compared to healthy controls, PCOS patients with hypothyroidism demonstrated a unique profile characterized by elevated cholesterol and triglycerides but notably higher HDL and lower LDL levels. Furthermore, hormonal analyses revealed lower FSH levels in PCOS patients without hypothyroidism, while those with hypothyroidism had diminished levels of complement C3, CTRP-5, and ASP. Correlation analyses indicated complex interrelationships among these biomarkers and metabolic parameters, suggesting that thyroid function may modulate the metabolic derangements associated with PCOS. The diagnostic potential of complement C3, CTRP-5, and ASP was affirmed through ROC curve analysis, indicating their utility in distinguishing PCOS patients from healthy individuals. Overall, these findings underscore the importance of considering thyroid status in the metabolic assessment and management of PCOS. Considering the metabolic changes in PCOS and the decrease in metabolic rate in hypothyroidism, it is suggested to investigate adipokines and its relationship with insulin resistance and BMI in both groups of PCOS patients with and without hypothyroidism.

Acknowledgements

Thanks to the members of the Biochemistry Department of Iran University of Medical Sciences who cooperated in conducting this study.

Author contributions

F.A and I.J.A .A. designed the project. F.A. conducted all tests. E.B. managed the project and analyzed the data. E.B. and F.A. wrote the main manuscript. The manuscript was revised by E.B and AH. the last revision was done by E.B. All authors reviewed and approved the manuscript.

Funding

This project was supported by the Iran University of Medical Sciences (Grant No. 26345).

Data availability

The datasets of the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures conducted in the study involving human participants adhered to the ethical standards set forth by the institutional and/or national research

committee and were aligned with the principles outlined in the 1964 Helsinki Declaration. The Ethics Commission at the Iran University of Medical Sciences assessed the project's adherence to the "Helsinki Laws" and approved the study (Ethical Code: IR.IUMS.REC.1402.669). Upon selecting a suitable participant following a thorough examination by a physician, she was invited to participate in the project. The project's objectives, procedures, including blood sampling, and the assurance of data confidentiality were explained to her, along with the option to withdraw from the study at any point of her choosing. Informed consent was obtained from all individual participants who were part of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 25 July 2024 / Accepted: 4 December 2024
Published online: 18 December 2024

References

1. Palomba S, de Wilde MA, Falbo A, Koster MP, La Sala GB, Fauser BC. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015;21(5):575–92.
2. Palomba S, Daolio J, La Sala GB. Oocyte competence in women with polycystic ovary syndrome. Trends Endocrinol Metab. 2017;28(3):186–98.
3. Palomba S, Piltonen TT, Giudice LC. Endometrial function in women with polycystic ovary syndrome: a comprehensive review. Hum Reprod Update. 2021;27(3):584–618.
4. Singla R, Gupta Y, Khemani M, Aggarwal S. Thyroid disorders and polycystic ovary syndrome: an emerging relationship. Indian J Endocrinol Metab. 2015;19(1):25–9.
5. Singh J, Wong H, Ahluwalia N, Go RM, Guerrero-Go MA, Metabolic. Hormonal, immunologic, and genetic factors Associated with the incidence of thyroid disorders in polycystic ovarian syndrome patients. Cureus. 2020;12(11):e11681.
6. Palomba S, Colombo C, Busnelli A, Caserta D, Vitale G. Polycystic ovary syndrome and thyroid disorder: a comprehensive narrative review of the literature. Front Endocrinol (Lausanne). 2023;14:1251866.
7. Fan H, Ren Q, Sheng Z, Deng G, Li L. The role of the thyroid in polycystic ovary syndrome. Front Endocrinol (Lausanne). 2023;14:1242050.
8. Kirkegaard S, Uldall Torp NM, Andersen S, Andersen SL. Endometriosis, polycystic ovary syndrome, and the thyroid: a review. Endocr Connect. 2024;13(2).
9. Rojhani E, Rahmati M, Firouzi F, Saei Ghare Naz M, Azizi F, Ramezani Tehrani F. Polycystic ovary syndrome, subclinical hypothyroidism, the cut-off value of thyroid stimulating hormone; is there a link? Findings of a Population-based study. Diagnostics (Basel). 2023;13(2).
10. Keen MA, Shah IH, Sheikh G. Cutaneous manifestations of polycystic ovary syndrome: a cross-sectional clinical study. Indian Dermatol Online J. 2017;8(2):104–10.
11. Chuan SS, Chang RJ. Polycystic ovary syndrome and acne. Skin Therapy Lett. 2010;15(10):1–4.
12. Mansour A, Mirahmad M, Mohajeri-Tehrani MR, Jamalizadeh M, Hosseinimousa S, Rashidi F, et al. Risk factors for insulin resistance related to polycystic ovarian syndrome in Iranian population. Sci Rep. 2023;13(1):10269.
13. Kar K, Sinha S. Variations of Adipokines and Insulin Resistance in primary hypothyroidism. J Clin Diagn Res. 2017;11(8):Bc07–9.
14. Schüler-Toprak S, Ortmann O, Buechler C, Treeck O. The Complex roles of Adipokines in Polycystic Ovary Syndrome and Endometriosis. Biomedicines. 2022;10(10).
15. Bongrani A, Mellouk N, Rame C, Cornuau M, Guérif F, Froment P et al. Ovarian expression of Adipokines in Polycystic Ovary Syndrome: a role for Chemerin, Omentin, and Apelin in follicular growth arrest and ovulatory dysfunction? Int J Mol Sci. 2019;20(15).
16. Kong M, Gao Y, Guo X, Xie Y, Yu Y. Role of the CTRP family in tumor development and progression. Oncol Lett. 2021;22(4):723.
17. Han J, Zhang X, Complement Component C. A novel biomarker participating in the pathogenesis of non-alcoholic fatty liver disease. Front Med (Lausanne). 2021;8:653293.
18. Ricklin D, Reis ES, Mastellos DC, Gros P, Lambris JD. Complement component C3 - the Swiss Army Knife of innate immunity and host defense. Immunol Rev. 2016;274(1):33–58.
19. Jia Q, Li C, Xia Y, Zhang Q, Wu H, Du H, et al. Association between complement C3 and prevalence of fatty liver disease in an adult population: a cross-sectional study from the Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIHealth) cohort study. PLoS ONE. 2015;10(4):e0122026.
20. Chen YK, Liu TT, Teia FKF, Xie MZ. Exploring the underlying mechanisms of obesity and diabetes and the potential of traditional Chinese medicine: an overview of the literature. Front Endocrinol (Lausanne). 2023;14:1218880.
21. Walsh MJ, Sniderman AD, Cianflone K, Vu H, Rodriguez MA, Forse RA. The effect of ASP on the adipocyte of the morbidly obese. J Surg Res. 1989;46(5):470–3.
22. Zhou L, Song K, Luo W. Association between circulating resistin levels and thyroid dysfunction: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2022;13:1071922.
23. Yu H, Yang Y, Zhang M, Lu H, Zhang J, Wang H, et al. Thyroid status influence on adiponectin, acylation stimulating protein (ASP) and complement C3 in hyperthyroid and hypothyroid subjects. Nutr Metab (Lond). 2006;3:13.
24. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, et al. Polycystic ovary syndrome. Nat Rev Dis Primers. 2016;2:16057.
25. Hata Y, Nakajima K. Application of Friedewald's LDL-cholesterol estimation formula to serum lipids in the Japanese population. Jpn Circ J. 1986;50(12):1191–200.
26. Benetti-Pinto CL, Piccolo VRSB, Garmes HM, Juliato CRT. Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal, and metabolic parameters. Fertil Steril. 2013;99(2):588–92.
27. Garelli S, Masiero S, Plebani M, Chen S, Furmaniak J, Armanini D, et al. High prevalence of chronic thyroiditis in patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reproductive Biology. 2013;169(2):248–51.
28. Kachuei M, Jafari F, Kachuei A, Keshteli AH. Prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Arch Gynecol Obstet. 2012;285:853–6.
29. Novais JSM, Benetti-Pinto CL, Garmes HM, Menezes Jales R, Juliato CRT. Polycystic ovary syndrome and chronic autoimmune thyroiditis. Gynecol Endocrinol. 2015;31(1):48–51.
30. Çalan M, Alan M, Alarslan P, Kocabaş GÜ, Bozkaya G, Acara AÇ, et al. Association of decreased C1q/tumor necrosis factorrelated protein-5 levels with metabolic and hormonal disturbance in polycystic ovary syndrome. J Turkish German Gynecol Association. 2019;20(2):89.
31. Ibrahim TAE-S, Ali AE-S, Radwan ME-H. Lipid profile in women with polycystic ovary syndrome. Egypt J Hosp Med. 2020;78(2):272–7.
32. Jiang F, Yang M, Zhao X, Liu R, Yang G, Liu D, et al. C1q/TNF-Related Protein5 (CTRP5) as a Biomarker to predict metabolic syndrome and each of its components. Int J Endocrinol. 2018;2018:7201473.
33. Majidi Z, Emamgholipour S, Omidifar A, Rahmani Fard S, Poustchi H, Shanaki M. The circulating levels of CTRP1 and CTRP5 are associated with obesity indices and carotid intima-media thickness (cIMT) value in patients with type 2 diabetes: a preliminary study. Diabetol Metab Syndr. 2021;13(1):14.
34. Emamgholipour S, Moradi N, Beigy M, Shabani P, Fadaei R, Poustchi H, et al. The association of circulating levels of complement-C1q TNF-related protein 5 (CTRP5) with nonalcoholic fatty liver disease and type 2 diabetes: a case-control study. Diabetol Metab Syndr. 2015;7:108.
35. Jiang F, Yang M, Zhao X, Liu R, Yang G, Liu D et al. C1q/TNF-related protein5 (CTRP5) as a biomarker to predict metabolic syndrome and each of its components. International journal of endocrinology. 2018;2018.
36. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Revett T, Gimeno R, Lodish HF. Molecular, biochemical and functional characterizations of C1q/TNF family members: adipose-tissue-selective expression patterns, regulation by PPAR-γ agonist, cysteine-mediated oligomerizations, combinatorial associations and metabolic functions. Biochem J. 2008;416(2):161–77.
37. Park S-Y, Choi JH, Ryu HS, Pak YK, Park KS, Lee HK, et al. C1q tumor necrosis factor α-related protein isoform 5 is increased in mitochondrial DNA-depleted myocytes and activates AMP-activated protein kinase. J Biol Chem. 2009;284(41):27780–9.
38. Wong GW, Wang J, Hug C, Tsao T-S, Lodish HF. A family of Acrp30/adiponectin structural and functional paralogs. Proceedings of the National Academy of Sciences. 2004;101(28):10302-7.
39. Schmid A, Kopp A, Aslanidis C, Wabitsch M, Müller M, Schäffler A. Regulation and function of C1Q/TNF-related protein-5 (CTRP-5) in the context of adipocyte biology. Exp Clin Endocrinol Diabetes. 2013;121(5):310–7.

40. Yang W-M, Lee W. CTRP5 ameliorates palmitate-induced apoptosis and insulin resistance through activation of AMPK and fatty acid oxidation. Biochem Biophys Res Commun. 2014;452(3):715–21.
41. Karkhaneh M, Qorbani M, Ataie-Jafari A, Mohajeri-Tehrani MR, Asayesh H, Hosseini S. Association of thyroid hormones with resting energy expenditure and complement C3 in normal weight high body fat women. Thyroid Res. 2019;12:1–6.
42. Klein JR. The immune system as a regulator of thyroid hormone activity. Experimental Biology Med. 2006;231(3):229–36.
43. Wu Y, Zhang J, Wen Y, Wang H, Zhang M, Cianflone K. Increased acylation-stimulating protein, C-reactive protein, and lipid levels in young women with polycystic ovary syndrome. Fertil Steril. 2009;91(1):213–9.
44. Chaker L, Razvi S, Bensenor IM, Azizi F, Pearce EN, Peeters RP, Hypothyroidism (Primer), editors. Nature Reviews: Disease Primers. 2022;8(1).
45. Singla R, Gupta Y, Khemani M, Aggarwal S. Thyroid disorders and polycystic ovary syndrome: an emerging relationship. Indian J Endocrinol Metabol. 2015;19(1):25.
46. Sinha U, Sinharay K, Saha S, Longkumer TA, Baul SN, Pal SK. Thyroid disorders in polycystic ovarian syndrome subjects: a tertiary hospital based cross-sectional study from Eastern India. Indian J Endocrinol Metabol. 2013;17(2):304.
47. Delitala AP, Scuteri A, Fiorillo E, Lakatta EG, Schlessinger D, Cucca F. Role of Adipokines in the association between thyroid hormone and components of the metabolic syndrome. J Clin Med. 2019;8(6).
48. Delitala AP, Steri M, Fiorillo E, Marongiu M, Lakatta EG, Schlessinger D, et al. Adipocytokine correlations with thyroid function and autoimmunity in euthyroid sardinians. Cytokine. 2018;111:189–93.
49. Yu H, Yang Y, Zhang M, Lu H, Zhang J, Wang H, et al. Thyroid status influence on adiponectin, acylation stimulating protein (ASP) and complement C3 in hyperthyroid and hypothyroid subjects. Nutr Metabolism. 2006;3:1–8.
50. Nath CK, Barman B, Das A, Rajkhowa P, Baruah P, Baruah M, Baruah A. Prolactin and thyroid stimulating hormone affecting the pattern of LH/FSH secretion in patients with polycystic ovary syndrome: a hospital-based study from North East India. J Family Med Prim Care. 2019;8(1):256–60.
51. Padalkar RK, Patil SM, Andure DV, Bhagat SS, Raut AM. Study of hormone and lipid profile in polycystic ovarian syndrome women between the age 18 to 30 years. J Pract Biochem Biophys. 2017;2:11–5.
52. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol. 2017;176(2):253–65.
53. Ghoraishian SM, Moghaddam SHH, Afkhami M. Relationship between anti-thyroid peroxidase antibody and thyroid function tests. World J Med Sci. 2006;1:44–7.

Publisher's note