RESEARCH LETTER

Relationship between serum gonadotropin concentrations and thyroid volume in women with polycystic ovary syndrome

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Introduction Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder, which affects about 5% to 10% of women in the reproductive age.[1] Women with PCOS may be characterized by clinical and biochemical hyperandrogenism, oligo, and anovulation and characteristic image of the ovaries on ultrasound. Therefore, PCOS is connected with reproductive, metabolic, cardiovascular, and psychological disturbances.[1] Despite a number of studies, the etiology of PCOS is still unknown. In a recently published genome-wide association study, it has been shown that gonadotrophins play a crucial role in the pathogenesis of PCOS.[2] Women with PCOS may show an elevated serum luteinizing hormone (LH) concentration and a relatively decreased serum follicle-stimulating hormone (FSH) level.[3]

LH and FSH are members of the glycoprotein family of hormones, which includes also human chorionic gonadotrophin (hCG) and thyroid-stimulating hormone (TSH). Moreover, these glycoprotein hormones have a similar alpha subunit and hormone-specific beta subunit.[4] There have been studies indicating that LH could increase thyroid adenylate cyclase activity in membranes of human thyroid cells.[5,6]

A positive correlation of thyroid volume (TV) with age, body surface area, and body mass index (BMI) was observed in a previous study.[7] As regards PCOS, it is very often accompanied by obesity.[1]

Based on a number of studies showing that PCOS is related to disturbances in thyroid function and structure, we tested the hypothesis of whether the hormonal profile is connected with TV in women with PCOS. Therefore, the aim of the present study was to evaluate a relationship between TV and serum levels of LH, FSH, testosterone, and estradiol in women suffering from PCOS compared with the control group.

Subjects and methods The study included 70 women: 36 with PCOS and 34 controls matched for age and BMI. PCOS was diagnosed according to the diagnostic criteria of the 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group, described in the previous study.[3] Women with PCOS were recruited from the Department of Reproduction and Gynecological Endocrinology, Medical University of Bialystok, Białystok, Poland. Control subjects were recruited using advertisement. All participants were nonsmokers.

The exclusion criteria were as follows: thyroid disorders (eg, hypothyroidism, hyperthyroidism, or any changes in the function and structure of the thyroid gland, such as hypoechogenity, heterogenity, or nodular diseases), smoking, morbid obesity, cardiovascular disease, diabetes, infections, hyperprolactinemia, or other serious medical conditions. Moreover, participants taking any medications (eg, oral contraceptive drugs, any drugs affecting lipid and glucose metabolism, radioactive iodine, levothyroxine) were also excluded from the study.

A clinical examination, anthropometric measurements, body fat assessment using a bioelectric impedance analysis, and oral glucose tolerance test (OGTT) were performed as previously described.[3] The LH/FSH ratio was calculated. Thyroid ultrasound was performed to evaluate the structure and volume of the thyroid gland. All analyses were carried out after overnight fast. The tests were performed in the PCOS group 3 to 5 days after spontaneous menses or regardless of the cycle phase in the presence of amenorrhea. In women with regular cycles, the tests were performed during the early follicular phase (3–5 days) of their menstrual cycles.

All participants gave their written informed consent to be included in the study. The study

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protocol was approved by the Ethics Committee of the Medical University of Bialystok and was concordant with the Declaration of Helsinki.

Biochemical analyses The plasma glucose level was measured on the same day using the enzymatic reference method with hexokinase (Cobas c111, Roche Diagnostic Ltd., Rotkreuz, Switzerland). Serum insulin, testosterone, LH, FSH, prolactin, and estradiol concentrations were assessed as described previously.[3]

The serum TSH concentration was estimated with the immunoradiometric method (sensitivity, 0.025 μIU/ml; intra-assay coefficient variation [CV], 0.6%; interassay CV, 2.1%). The serum free triiodothyronine (FT_3) (sensitivity, 0.5 pmol/l; intra-assay CV, 6.4%; interassay CV, 5.5%) and serum free thyroxine (FT_4) (sensitivity, 0.4 pmol/l; intra-assay CV, 10.3%, interassay CV, 7.6%) concentrations were detected with radioimmunoassay kits (DIAsource ImmunoAssays S.A., Louvain-La-Neuve, Belgium). Antithyroperoxidase antibody (TPOAb) concentrations (sensitivity, 5.5 U/ml; intraassay CV, 3.9%; interassay CV, 4.1%) were measured with radioimmunoassay kits (DIAsource ImmunoAssays S.A.).

Thyroid ultrasound Ultrasound of the thyroid gland was performed with the use of 7.5-MHz linear transducer (Philips HD5 Diagnostic Ultrasound System, Bothell, Washington, United States; Neusoft Park, Hun Nan Industrial Area, Shenyang, China). TV was calculated using the following equation: (length × width × thickness of the lobes) × 0.479.[8]

Statistical analysis Statistical analyses were performed using the STATISTICA 10.0 software. The variables were tested for normal distribution using the Shapiro–Wilk test. Due to abnormal distribution of the data, all values were expressed as median and interquartile range. The differences between the groups were evaluated with the nonparametric Mann–Whitney test. The relationships between variables were evaluated using the Spearman rank correlation and multiple logistic regression analysis. The level of significance was accepted at a P value of less than 0.05.

Results The clinical and biochemical characteristics of the studied groups are shown in TABLE 1. No differences in age, anthropometric indices, glucose concentration at 0 and 120 minutes of the OGTT, thyroid volume, and serum FT_3, FT_4, TPOAb concentrations (all P >0.05) were found between women with PCOS and controls (TABLE 1). Women with PCOS had higher serum concentrations of testosterone (P = 0.01) and lower serum concentrations of FSH (P = 0.008) and TSH (P = 0.003) compared with the control group (TABLE 1). The LH/FSH ratio in women with PCOS was higher than that in the control group (P = 0.01).

No difference in mean TV between the studied groups was observed (P = 0.97) (TABLE 1). A positive correlation between TV and the LH/FSH ratio (r = 0.36; P = 0.02) was found only in women with PCOS (Supplementary material online, FIGURE 1). This correlation was still observed after adjustment for BMI (β = 0.33; P = 0.04). We also observed a negative correlation between TSH levels and the LH/FSH ratio (r = –0.34; P = 0.04) in the PCOS group. In the control group, TV correlated positively with serum estradiol levels (r = 0.50; P = 0.003); this correlation remained significant after adjustment for BMI. We observed a positive correlation between TV and BMI in the whole group (r = 0.28, P = 0.01). The stepwise multiple regression analysis with TV as a dependent variable revealed that only the LH/FSH ratio (β = 0.39, P = 0.02) and serum estradiol concentrations (β = –0.36, P = 0.03), taken together, explained 25% of TV variation in women with PCOS (R^2 = 0.25), without BMI in the regression model.

Discussion We observed that mean TV did not differ between young, lean women with PCOS and the control group without PCOS. However, we demonstrated a positive relationship between the LH/FSH ratio and TV in women with PCOS, but not in the control group. Moreover, TV positively correlated with BMI in the whole group.

Two recently published studies have reported a similar relationship (ie, a positive correlation between serum LH concentrations and TV in women with PCOS).[9,10] The authors concluded that elevated serum LH concentrations may lead to an increase in TV in women with PCOS. Also, it has been shown that these women are characterized by an imbalance between LH and FSH levels in comparison with healthy women.[11]

In the present study, women with PCOS had an elevated LH/FSH ratio in comparison with the control group. As mentioned above, LH binds to the TSH receptor and stimulates adenylate cyclase.[5,6] Moreover, it has been shown that LH inhibits TSH binding with thyroid follicular cells.[5] Nevertheless, the impact of gonadotrophins on TV is still unclear. It has been revealed that hCG could exert thyrotropic effects on the human thyroid cell membrane by stimulating iodide uptake, adenylate cyclase, and deoxyribonucleic acid synthesis in cultured rat thyroid cells.[12,13] LH was found to show strong structural and functional similarities to hCG.[5] Considering the above results, we can assume that the balance between LH and FSH levels is vital for thyroid function and could affect TV.

A study by Polat et al[9] showed that TV was higher in women with PCOS in comparison with the control group. However, we found no differences in TV between these groups in our study. The discrepancies may result from differences in the characteristics of the studied groups. In the above study, women with PCOS had higher BMI (29.3 ±7 kg/m^2) in comparison with the control group (25.2 ±5.2 kg/m^2).[9] Importantly, the authors showed that BMI was associated with TV.[9] We also observed a positive correlation between

TABLE 1 Clinical and biochemical characteristic of the studied groups

Parameters		Control group (n = 34)	PCOS (n = 36)	*P* value
age, y		25.0 (6.0)	24.5 (4.0)	0.87
body weight, kg		61.1 (12.4)	65.6 (12.6)	0.22
BMI, kg/m^2		21.6 (3.2)	22.8 (5.8)	0.15
waist circumference, cm		78.0 (11.0)	78.0 (14.0)	0.90
hip circumference, cm		95.5 (10.0)	95.0 (10.0)	0.53
FFM, kg		43.4 (9.0)	44.4 (4.3)	0.23
FM, kg		16.4 (8.6)	20.4 (11.5)	0.42
glucose, mg/dl	0′ OGTT	93.0 (6.0)	92.5 (7.5)	0.34
	120′ OGTT	97.0 (21.0)	93.0 (25.0)	0.32
fasting insulin, μIU/ml		9.7 (5.5)	8.4 (5.7)	0.80
LH, mIU/ml		4.4 (1.7)	4.5 (2.5)	1.0
FSH, mIU/ml		6.0 (2.5)	4.9 (2.1)	0.008
LH/FSH ratio		0.65 (0.35)	0.88 (0.57)	0.01
estradiol, pg/ml		45.0 (53.3)	45.3 (56.9)	0.58
testosterone, ng/ml		0.49 (0.29)	0.63 (0.29)	0.01
prolactin, ng/ml		9.9 (6.9)	10.2 (11.35)	0.56
TSH, IU/ml		1.735 (0.938)	1.375 (0.759)	0.003
FT_4, ng/dl		1.273 (0.165)	1.256 (0.250)	0.79
FT_3, pg/ml		2.427 (0.554)	2.480 (0.678)	0.58
TV, ml		10.1 (4.3)	10.6 (4.7)	0.97

Data are presented as median (interquartile range). Differences between the groups are derived from the nonparametric Mann–Whitney test. *P* value: PCOS women vs the control group.

Abbreviations: BMI, body mass index; FM, fat mass; FFM, fat-free mass; FT_3, free triiodothyronine; FT_4, free thyroxine; FSH, follicle-stimulating hormone; LH, luteinizing hormone; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone; TV, thyroid volume

TV and BMI in the whole group. However, in our study, women with PCOS and the control group were matched for BMI. Therefore, it may explain why we observed no differences in TV between the studied groups. Based on our findings and the results reported by other authors,[7] it seems that TV should not be compared in groups with different BMI.

In our study, we observed that women with PCOS have lower serum TSH concentrations in comparison with the control group. In some previous studies, the higher incidence of Hashimoto thyroiditis and higher serum TSH levels were observed in women with PCOS in comparison with the control group.[14,15] The higher serum TSH level in those studies probably results from the fact that PCOS and control groups were not matched for BMI.[14,15] In our study, we examined the groups with a lower BMI and matched for BMI. Therefore, we can hypothesize that elevated serum TSH levels observed by other investigators can be associated with obesity in women with PCOS or by higher incidence of Hashimoto thyroiditis. Moreover, we included women without any thyroid disorders. Additionally, our groups did not differ in terms of the serum TPOAb concentration (P = 0.5).

In conclusion, our study showed a correlation between the LH/FSH ratio and TV in women with PCOS, although a relatively small number of participants is a considerable limitation that should be considered when interpreting the results of the study.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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