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PCOS AND AUTOIMMUNE THYROIDITIS

Polycystic ovary syndrome and chronic autoimmune thyroiditis

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) has been associated with an autoimmune origin, either per se or favoring the onset of autoimmune diseases, from a stimulatory action on the inflammatory response. Thus, autoimmune thyroiditis (AIT) could be more prevalent among women with PCOS.
Objective: To evaluate the prevalence of AIT in women with PCOS.
Study design: It was a cross-sectional study, in a tertiary center, including 65 women with PCOS and 65 women without this condition. Clinical and laboratory parameters were evaluated and a thyroid ultrasound scan was performed. Levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase (anti-TPO) antibodies, anti-thyroglobulin (anti-TG) antibodies, and thyroid ultrasound findings were evaluated.
Results: The prevalence of subclinical hypothyroidism (SCH) in women with PCOS was 16.9% and 6.2% in the non-PCOS group. AIT was more common in the PCOS group compared with the non-PCOS group (43.1% versus 26.2%). But, when it was adjusted by weight and insulin resistance, the difference in the thyroiditis risk was not observed (OR 0.78, CI 0.28–2.16).
Conclusion: AIT risk was similar in the PCOS and the non-PCOS group. SCH are more common in women with PCOS, highlighting a need for periodic monitoring of thyroid function.

Keywords

Anti-thyroid peroxidase, anti-thyroglobulin, autoimmune thyroiditis, polycystic ovary syndrome, subclinical hypothyroidism

History

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Introduction

Polycystic ovary syndrome (PCOS) is an endocrine and metabolic disorder that affects around 10% of women of reproductive age [1]. In women with PCOS, the relative predominance of estrogen over progesterone is believed to be associated with an exacerbated inflammatory response that favors the onset of autoimmune diseases [2].

Chronic autoimmune thyroiditis (AIT) is the principal autoimmune disease in women of reproductive age [3]. Diagnosis is based on the presence of anti-peroxidase (anti-TPO) antibodies and/or anti-thyroglobulin (anti-TG) antibodies and hypoechogenicity of the thyroid gland at ultrasound [4–6]. Histology typically shows a lymphocytic infiltrate and fibrosis of the glandular parenchyma, which is the gold standard for diagnosis [7]. Recent studies on the association between AIT and PCOS have shown conflicting results [4,8–11].

In a sample of women with PCOS, the prevalence of subclinical hypothyroidism (SCH) was shown to be 11%, higher than that reported for young women in general [5]. The principal cause of SCH is known to be AIT [6]. Considering the high frequency of SCH and the association between PCOS and autoimmunity, the objective of the present study was to evaluate the prevalence of AIT in a sample of women with PCOS.

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Materials and methods

Subjects

The study was conducted at the Department of Obstetrics and Gynecology, School of Medical Sciences, University of Campinas (UNICAMP) between August 2012 and August 2013. The institutional review board approved the protocol, and all the participants signed an informed consent form. This was a cross-sectional study involving 130 women, 65 of whom had received a diagnosis of PCOS. Diagnosis was reached according to the Rotterdam criteria, whenever two of the three following features were detected: oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries at ultrasound [12]. The exclusion criteria consisted of previously diagnosed thyroid disease, late-onset congenital adrenal hyperplasia, androgen-secreting tumors, hyperprolactinemia, and kidney or liver disease.

The comparing group consisted of 65 women without PCOS. These women were receiving care at the family planning clinic and had been in the use of a copper T intrauterine device (IUD) for at least 6 months. They had regular menstrual cycles of 24–32 d [13] and showed no clinical signs of hyperandrogenism, i.e. no hirsutism according to the Ferriman–Gallwey score [14]. The exclusion criteria for this group consisted of previously diagnosed thyroid disease and kidney or liver disease.

Clinical evaluation

Weight and height were measured and body mass index (BMI kg/m^2) was calculated for all the women. Hirsutism was classified in accordance with the Ferriman–Gallwey score, which was based on the nine areas of the human body, rated on a scale of

1–4 according to the amount of body hair in each area. The final score is calculated from the sum of the scores attributed to these nine body areas, with values ≥ 8 being considered indicative of hirsutism [14].

Laboratory tests

All the women were submitted to the following tests: thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-TPO, and anti-TG antibodies measured by electrochemiluminescence (Cobas e611, Roche, Mannhein, Germany) [15].

Clinical hypothyroidism was defined as FT4 levels below the lower normal limit of 0.9 ng/dl and TSH values above 10 mIU/l, while SCH was defined as TSH values between 4.5 and 10 mIU/l together with normal FT4 levels (0.9–1.8 ng/dl) [16,17].

A diagnosis of AIT was made when two of the three following factors were present: positivity for anti-TPO and/or anti-TG antibodies, hypoechogenicity of the thyroid gland at ultrasound, and TSH levels above the value considered normal [8].

Insulin resistance (IR) was also evaluated using the homeostatic model assessment of insulin resistance (HOMA-IR), which represents an indirect evaluation of IR made by measuring endogenous insulin and glucose after a 12-h fasting period. HOMA-IR ≥ 2.71, the cut-off point established for a diagnosis of IR in the Brazilian population, was defined as the cut-off point for the present study [5,16].

Ultrasonography

Ultrasonography was performed using an ultrasound system equipped with a 4–10 MHz linear transducer (Voluson 730 Expert General Electrics, Bucks, United Kingdom). Thyroid echogenicity was considered to be reduced when it was similar to or lower than that found in the surrounding neck muscles. Thyroid volume was calculated, with values of 6–14 ml being considered normal [18,19]. The same examiner performed all the scans.

Sample size and statistical analysis

The calculation of sample size was based on the prevalence of anti-TPO and anti-TG antibodies, as well as on ultrasound findings suggestive of thyroiditis in women with and without PCOS. Considering the differences between the reported prevalence rates [4], a significance level of 5% and a test power of 80%, the sample size was calculated at 130 subjects, 65 women with PCOS and 65 without PCOS [20].

The results were presented as mean ± standard deviation. Analysis were performed using Student's *t*-test, the χ^2 test, Fisher's exact test, the Mann–Whitney test, and by estimating odds ratios. The logistic multiple regressions were used to calculate the adjusted odds ratio by weight and insulin resistance [20].

Results

The 130 participants in this study were young women of 18–40 years of age. The mean age of the women in the PCOS group ($N = 65$) was 27.8 ± 6.9 years compared with 33.5 ± 5.7 years for the women without PCOS ($N = 65$) ($p < 0.0001$). Mean BMI of the women in the PCOS group was 34.8 ± 8.9 kg/m^2 compared with 28.4 ± 4.8 kg/m^2 for those in the comparing group ($p < 0.0001$). The Ferriman–Gallwey score for the PCOS and without PCOS groups was 8 ± 3.1 and 5 ± 0.7, respectively ($p < 0.0001$) (Table 1).

Mean TSH values were 2.9 ± 1.8 mIU/l in the PCOS group and 2.2 ± 1.2 mIU/l in the group without PCOS ($p = 0.0133$) (Table 1). The prevalence of SCH was 16.9% (11/65 women) in the PCOS group and 6.2% (4/65 women) in the group without PCOS, with odds ratio of 3.10 (OR 3.10, CI 0.93–10.31). Even after adjustment by weight and insulin resistance, the risk of SCH was 4.69 higher in the PCOS group, when compared with the non-PCOS group (CI 1.12–19.61).

Table 1. Clinical features of the women in the PCOS and non-PCOS groups.

Variables	PCOS ($n = 65$)	Non-PCOS ($n = 65$)	p Value
Age (years)*	27.8 ± 6.9	33.5 ± 5.7	<0.0001
BMI (kg/m^2)	34.8 ± 8.9	28.4 ± 4.8	<0.0001
Ferriman–Gallwey score	8.3 ± 3.1	5.1 ± 0.7	<0.0001
TSH (mIU/l)	2.9 ± 1.8	2.2 ± 1.2	0.0133
FT4 (ng/dl)*	1.18 ± 0.17	1.17 ± 0.15	0.7118
FT3 (ng/dl)	0.34 ± 0.05	0.32 ± 0.04	0.0020

Mean ± standard deviation; Mann–Whitney test.
BMI, Body Mass Index; TSH, thyroid-stimulating hormone; FT4, free thyroxin; FT3, free triiodothyronine.
*Student's *t*-test.

There was no difference between the two groups with respect to the presence of anti-TPO or anti-TG antibodies. With respect to thyroid volume, as evaluated by ultrasonography (data not shown), there was no difference between the groups. The glands were a little more hypoechoic in the PCOS group (26.8% versus 15.4%; $p = 0.05$); however, this difference was not confirmed after adjustment by weight and insulin resistance between the two groups.

When AIT was diagnosed according to the criteria defined by Garelli et al. [8], a significant difference was found in its prevalence, with 43.1% of thyroiditis in the PCOS group compared with 26.2% in the group without PCOS ($p = 0.04$). The odds ratio of AIT in the PCOS group was 2.14 (CI 1.02–4.48). When adjusted by weight and insulin resistance, the odds ratio was 0.78 (CI 0.28–2.16) (Table 2).

Discussion

The gold standard for diagnosis of AIT is the histological evaluation of the thyroid. Because it is a relatively invasive procedure, some authors use clinical and ultrasound criteria for this diagnosis. Our study, considering the criteria proposed by Garelli for AIT, revealed a prevalence rate of chronic AIT of 43.1% in the PCOS group, a rate that was significantly higher than that found in the group without PCOS (26.2%). The estimated risk of AIT was twice as high in the presence of PCOS, but the results were not confirmed when the analysis was adjusted for weight and insulin resistance, factors associated with a higher prevalence of thyroid dysfunction [3,5,6,17,21].

This study found a prevalence of 16.9% of SCH in young women with PCOS and 6.2% in women without this condition. These values are higher than the rate of SCH of 2% reported in the literature for young women [6], but in agreement with the previously reported by others investigators, showing a prevalence of 11.3% of SCH in a similar population with PCOS [5]. The importance of the higher prevalence of SCH in the population with PCOS lies in the fact that SCH intensifies the already established metabolic repercussions of PCOS [3,21].

Recently, a possible intersection between AIT and PCOS was investigated. It has been speculated that this association may be the consequence of the relative predominance of estrogen over progesterone, a characteristic of PCOS that triggers an exacerbated immune response, hence the appearance of autoimmune diseases [2,22,23].

In relation with the presence of anti-TPO and anti-TG antibodies, no significant difference was found in positivity

Table 2. Anti-TPO/anti-TG antibodies, hypoechogenicity at thyroid ultrasound (US), and autoimmune thyroiditis in the PCOS and non-PCOS groups.

Variables	PCOS ($N=65$), N (%)	Non-PCOS ($N=65$), N (%)	p Value	Crude odds ratio (IC 95%)	Adjusted odds ratio (IC 95%)
ATPO			0.3444		
Positive	7 (10.8)	4 (6.2)		1.84 (0.51–6.62)	1.62 (0.35–7.52)
Negative	58 (89.2)	61 (93,8)		1.00	1.00
ATG			0.7527		
positive	6 (9.2)	5 (7.7)		1.22 (0.35–4.22)	2.21 (0.47–10.42)
negative	59 (90.8)	60 (92.3)		1.00	1.00
Both			0.5445		
positive	7 (8.5)	5 (6.7)		1.45 (0.43–4.82)	1.83 (0.42–8.00)
negative	58 (70.7)	60 (80.0)		1.00	1.00
Hypoechogenicity US	17 (26.8)	10 (15.4)	0.0522*	0.24 (0.01–5.08)	0.78 (0.28–2.16)
AIT†	28 (43.1)	17 (26.2)	0.04	2.14 (1.02–4.48)	0.78 (0.28–2.16)

*Fisher exact test/odds ratio adjusted by weight and HOMA.
†AIT according to Garelli criteria.

between the women with and without PCOS, which was in agreement with other reports. A study involving 165 women with and without PCOS also failed to find any difference in relation to the presence of these antithyroid antibodies [9]. Another study comparing the presence of antithyroid antibodies in women with PCOS and in women without this condition showed higher titers only for anti-TPO antibodies in the PCOS group when absolute values were analyzed [10]. Nevertheless, this difference was not confirmed when these titers were classified as positive or negative [10].

The gold standard for diagnosis of AIT is a cytological finding of lymphocytic infiltration of the gland at punch biopsy [7]. Notwithstanding, punch biopsy of the thyroid is known to be an invasive method and one that is subject to complications [19]. Therefore, efforts are made to use alternative methods such as thyroid ultrasound to diagnose chronic AIT in an attempt to reduce the likelihood of complications. Although antithyroid antibody testing is a fundamental part of the investigative process in suspected cases of chronic AIT, this method should not be used alone to define AIT.

Our results, as well as others in the literature, show an association between HSC and PCOS [3,5,6,17,21]. The main cause of HSC is AIT [7,17–19]. Our results failed to demonstrate association of PCOS and AIT, according to the criteria proposed by Garelli (clinical and ultrasonographic criteria). A limitation of the study that could have affected this finding is the inherent subjectivity of ultrasonography [18]. Future studies using punch biopsy and cytological evaluation of the thyroid may contribute towards evaluation of the association between thyroiditis and PCOS.

Conclusion

This study failed to show a higher thyroiditis risk in PCOS women. Future studies could elucidate this association. However, the higher prevalence of SCH found in this group should serve as an alert to the importance of monitoring thyroid function in women with PCOS.

Declaration of interest

The authors report that they have no declarations of interest.

References

1. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997;18:774–800.
2. Gleicher N, Barad D, Weghofer A. Functional autoantibodies, a new paradigm in autoimmunity? Autoimmun Rev 2007;7:42–5.
3. Mueller A, Schöfl C, Dittrich R, et al. Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome. Hum Reprod 2009;24:2924–30.
4. Janssen OE, Mehlmauer N, Hahn S, et al. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol 2004;150:363–9.
5. Benetti-Pinto CL, Berini Piccolo VR, Garmes HM, Teatin Juliato CR. Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal, and metabolic parameters. Fertil Steril 2013;99:588–92.
6. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet 2012;379:1142–54.
7. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med 1996;335:99–107.
8. Garelli S, Masiero S, Plebani M, et al. High prevalence of chronic thyroiditis in patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2013;169:248–51.
9. Anaforoglu I, Topbas M, Algun E. Relative associations of polycystic ovarian syndrome vs. metabolic syndrome with thyroid function, volume, nodularity and autoimmunity. J Endocrinol Invest 2011;34:e259–64.
10. 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.
11. Ganie MA, Marwaha RK, Aggarwal R, Singh S. High prevalence of polycystic ovary syndrome characteristics in girls with euthyroid chronic lymphocytic thyroiditis: a case-control study. Eur J Endocrinol 2010;162:1117–22.
12. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
13. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil 1967;12:77–126.
14. Archer JS, Chang RJ. Hirsutism and acne in polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2004;18:737–54.
15. Babson AL. The immulite automated immunoassay system. J Clin Immunoassay 1991;14:83–8.
16. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–19.
17. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228–38.
18. Pedersen OM, Aardal NP, Larssen TB, et al. The value of ultrasonography in predicting autoimmune thyroid disease. Thyroid 2000;10:251–9.
19. Sheth S. Role of ultrasonography in thyroid disease. Otolaryngol Clin North Am 2010;43:239–55.
20. Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective on their design, analysis, and interpretation. Control Clin Trials 1997;18:530–45.