

Autoimmune Thyroid Disease in Patients with Polycystic Ovary Syndrome: The Role of Sexual Hormones

Mailson Batista Fernandes^{1*} & Aljerry Dias do Rêgo^{1,2}

¹*Faculty of Medicine, Federal University of Amapá, Amapá, Brazil*

²*Department of Gynecology, Faculty of Medicine, Federal University of Amapá, Amapá, Brazil*

***Correspondence to:** Dr. Mailson Batista Fernandes, Faculty of Medicine, Federal University of Amapá, Amapá, Brazil.

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Abstract

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women in the menacme and involves complex pathophysiology, with genetic, metabolic and hormonal factors acting synergistically. Its endocrine-metabolic characteristics have been related to changes in thyroid physiology. PCOS and autoimmune/hormonal thyroid disease are disorders related to increased cardiovascular morbidity and mortality, making it necessary to assess the prevalence of thyroid dysfunction in PCOS patients; and what pathophysiological mechanisms of this, especially related to sexual hormones, can favor the appearance and progression of that one.

Methods

It is a review of scientific articles, searched in the MEDLINE database, through PUBMED, published in English between January 2010 and April 2018.

Results

The prevalence of autoimmune thyroiditis (AIT) and higher levels of thyroid stimulating hormone (TSH) is higher among carriers of PCOS. Patients with PCOS may develop thyroid disease due to genetic predisposition; changes in metabolic profile such as insulin resistance and chronic inflammation; and changes in hormonal profile due to an increase in estrogen/progesterone ratio causing susceptibility to autoimmunity and development of antithyroid antibodies through an increase of the inflammatory cytokines and decrease of inhibitory mechanisms on the immune system.

Conclusions

Due to the strong association between PCOS and AIT, it is recommended to screen for antithyroid antibodies and to monitor thyroid function in the follow-up of women with PCOS. Management of the metabolic syndrome allows control of the chronic inflammation that may impact on thyroid function. Treatment of oligoanovulatory cycles may reduce the risk of onset and/or progression of AIT related to dysfunction on estrogen/progesterone ratio.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women of reproductive age, with a prevalence of 5-10% according to the Rotterdam criteria of 2003 [1]. Based on these criteria, the diagnosis of PCOS is established from at least two of the following three discoveries: polycystic ovary through pelvic ultrasound; hyperandrogenism (clinical and/or biochemical); and oligovulation and/or anovulation [2], after excluding other differential diagnoses such as hyperandrogenic syndrome (congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome) and prolactinomas [2,3]. The disorder is characterized by an endocrine and metabolic profile that contributes to the early pathogenesis of atherosclerosis and an increase in cardiovascular risk, with dyslipidemia, metabolic syndrome, insulin resistance and type 2 diabetes mellitus [4,5], with reproductive implications, being the most frequent cause of female infertility due to anovulation being frequently associated with menstrual irregularities [6], besides having psychological repercussions [7].

Thyroid dysfunctions are also among the most common endocrine diseases in the general population [5]. Hypothyroidism is a known cause of clinical profile with manifestations similar to those of PCOS [8]. Hypothyroidism can affect gonadal function and fertility [4], being able to increase ovarian sensitivity to the action of gonadotropins and cause hypertrophy of the ovaries and also the formation of multiple follicular cysts. In addition, it can cause menstrual irregularities and ovulatory dysfunction [6]. For this reason it is necessary to exclude the possibility of hypothyroidism before the diagnosis of PCOS [8].

Autoimmune thyroiditis (AIT), the main form of which is Hashimoto's thyroiditis (HT), also called chronic lymphocytic thyroiditis, is the most frequent cause of autoimmune disease; and hypothyroidism [9], due to the destruction and fibrosis of parenchymal tissue [10]. AIT affects 5-20% of the young female population

and is the main cause of hypothyroidism in women [10]. The gold standard for the diagnosis of HT is based on histological examination, with findings of fibrosis and lymphocytic infiltration, although currently such examination is not done routinely because it is invasive and due to availability and cost [9]. Thus, the diagnosis has been made from the detection of high levels of anti-thyroperoxidase antibody (anti-TPO) and/or anti-thyroglobulin antibody (anti-Tg) in the serum and a thyroid image characteristic of ultrasound - hypoechoogenicity or heterogeneous echotexture [9]. Subclinical hypothyroidism (SCH) is defined as high levels of thyroid stimulating hormone (TSH) with normal levels of free thyroxine (FT4). However, the diagnosis of SCH is dependent on the definition of upper limit of TSH, which remains a topic of debate [1]. The prevalence of hypothyroidism considering TSH above 4.5mIU/L in women of reproductive age is about 4% and the percentage increases with advancing age. Therefore, thyroid dysfunctions among young women are more likely to be represented by normal hormonal function with findings suggestive of progressing autoimmune disease (high titers of thyroid antibodies and/or characteristic sonographic imaging) [9].

There is a growing body of evidence demonstrating that thyroid autoimmunity and thyroid hormone dysfunction are more common in women with PCOS than in non-PCOS patients [2,3,11,12,13], especially subclinical hypothyroidism (SCH) [11]. However, the mechanism of association is still uncertain [5]. Several similar factors, such as genetic susceptibility and inflammation/autoimmunity, contribute to the pathogenesis of PCOS and thyroid dysfunction, suggesting a potential pathophysiological link between the two diseases [12]. In addition, factors related to sex hormones could stimulate autoimmune response and, thus, favor the development of autoimmune disorders in women [6].

Considering the growing evidence of AIT and hypothyroidism in patients with PCOS, the present study aims to evaluate the prevalence of the association between thyroid disease and PCOS; and to review the possible pathophysiological factors involved, with emphasis on sex hormones.

Methods

This is a review of scientific articles, searched in the Medical Literature and Retrieval System on Line database (MEDLINE), through PUBMED, using a search with the following descriptors: (PCOS [title] OR polycystic ovary syndrome [title]) AND (thyroid [title] OR thyroiditis [title] OR autoimmune [title] OR autoimmunity [title] OR hypothyroidism [title] OR TSH [title]). All included articles were published in English language and between January 2010 and April 2018, the complete text of which was available. We excluded studies that did not meet the inclusion criteria previously mentioned.

Thyroid Disease in Patients with PCOS

Recent studies have demonstrated an association between polycystic ovary syndrome (PCOS) and hypothyroidism [5]. Gaberšček *et al.* [6] in their review study cite that the first systematic prospective study [14] addressing the prevalence of AIT in women with PCOS included 168 healthy controls and 175 women with PCOS, with a mean of 28 years; and that in this study we found a prevalence of 26.9% of positivity for anti-TPO and/or anti-Tg antibodies in those with PCOS against 8.3% of positivity in the control group. Since TSH levels were significantly higher among those with PCOS, the hypoechoic ultrasound pattern characteristic of HT was present in 42.3% of these patients versus 6.5% in women without PCOS [6]. In

this study, 36 of the 175 patients with PCOS had established HT (20.6%), while only 11 of the 168 women in the control group had HT (6.5%). Thus, the prevalence of autoimmune thyroid disease, specifically HT, was about three times higher in women with PCOS when compared to controls [6].

An Italian study developed by Garelli *et al.* [13] to evaluate the prevalence of autoimmune thyroid disease and other non-organ autoimmune pathologies in 113 women with PCOS described a higher prevalence of AIT in these patients compared to 100 patients in the group control (27% versus 8%, $p < 0.001$). In the mentioned study, AIT was present in 30/113 patients with PCOS. Of these 30 patients, the typical ultrasound pattern of thyroiditis was observed in 28 patients; the presence of two antithyroid antibodies (anti-TPO and anti-Tg) was detected in 16 patients; in 10 patients there was only anti-TPO; and in 2 patients they had only anti-Tg positive antibody. All 30 patients with associated PCOS and AIT had normal levels of free T4 and only one had subclinical hypothyroidism [13].

Muscogiuri *et al.* [15] performed a study with 50 women with PCOS to investigate the association of AIT and levels of 25 (OH) vitamin D. In this study AIT was diagnosed when anti-TPO antibodies exceeding 80U/ml and/or anti-Tg antibodies levels exceeding 70U/ml. It was observed a prevalence of 24% AIT in the patients studied [15]. Furthermore, 25 (OH) vitamin D levels were significantly lower in AIT patients when compared with patients without AIT (32.0 ± 22.6 versus 49.6 ± 19.9 nmol/L; $p = 0.02$) [15].

In the original study by Benetti-Pinto *et al.* [16], where 168 Brazilian women with PCOS were recruited, with an age average of 24 years, prevalence of subclinical hypothyroidism (SCH) was observed in 11.3% of these patients. Since SCH is a condition found in approximately 4% to 10% of the general population, being about 2% in young women between 12 and 39 years old, it can be said that the prevalence found in this study was higher than expected [16].

Duran *et al.* [17], on the other hand, did not find evidence of association of AIT and PCOS in their study group composed of 73 women with PCOS and 60 age-adjusted controls. If positivity of antithyroid autoantibodies and/or thyroid heterogeneity were considered as criteria for AIT, the frequency of autoimmune dysfunction in those with PCOS was 32.5% versus 23.3% in those in the control group, with no statistically significant difference ($p = 0.394$). In their work, the authors suggest studies with larger samples and with objective and standardized modalities of laboratory and image [17].

In a study conducted by Arduc *et al.* [12] to investigate the relationship between PCOS and HT and the possible effects of endocrine-metabolic factors of PCOS on thyroid autoimmunity, 86 women with PCOS and 60 women without PCOS who body mass index (BMI). Women with PCOS had significantly higher levels of anti-TPO and anti-Tg when compared to the control group ($p = 0.017$ and $p = 0.014$, respectively). Anti-TPO levels were positive in 23 (26.7%) of the 86 patients with PCOS compared to only 4 (6.6%) positive in the control group ($p = 0.002$). Positivity for anti-Tg was found in 14 (16.2%) of the PCOS group versus 3 (5%) in the control group ($p = 0.039$). HT was detected in 19 (22.1%) of those with PCOS and in only 3 (5%) of the control group ($p = 0.004$). Finally, TSH levels were higher in the PCOS group than in the control group ($p = 0.037$) [12].

Kachuei *et al.* [10] in a case-control study with 78 patients with PCOS and 350 in the control group, observed significantly higher anti-TPO levels among those with PCOS ($p = 0.040$). However, the anti-TPO positivity did not differ between the case and control groups, with respectively 30.6% and 27.8% ($p = 0.730$). Anti-Tg levels were not statistically significant ($p = 0.467$), and although the anti-Tg positivity was higher among those with PCOS than among the control group (36.4% versus 30%), this finding was not significant ($p = 0.467$). TSH levels also did not differ significantly between patients with PCOS and women in the control group (2.77 ± 3.8 IU/mL versus 2.29 ± 1.5 IU/mL, $p = 0.09$). The authors suggest further studies and that larger samples may result in more statistically significant results [10].

In the original study by Yu and Wang [3], 100 women diagnosed with PCOS and 100 women in the control group, matched for age and body mass index (BMI), were evaluated in order to analyze thyroid dysfunctions in these groups of patients. In this study, it was observed that PCOS is associated with a high incidence of AIT and subclinical hypothyroidism (SCH) [3]. Significant levels of TSH ($p < 0.001$) and anti-TPO ($p < 0.01$) and lower triiodothyronine, also known as T₃, ($p < 0.001$) were found in the group of women with PCOS compared to the control group. T₄ levels were slightly lower in women with PCOS, but without statistical significance. In addition, in this study the ultrasound finding of characteristic hypoechogenicity was significantly higher in women with PCOS compared to controls (34% versus 7%, $p < 0.01$). AIT, whose diagnosis in the aforementioned study was based on the presence of anti-TPO antibody associated with hypoechogenicity on ultrasound examination, was more prevalent and significantly in the PCOS group in relation to control (25% versus 2%, $p < 0.001$) [3]. As for thyroid hormone dysfunctions, women with PCOS also had a significantly higher prevalence. Overt hypothyroidism was present in 3% of the women with PCOS and in no individual in the control group ($p < 0.01$); and subclinical hypothyroidism was observed in 27% of the PCOS group versus 8% in the control group ($p = 0.0002$). The state of euthyroidism was markedly higher in those in the control group than in women with PCOS (91% versus 68%, $p < 0.0001$). There was no statistical difference regarding hyperthyroidism [3].

From the majority of studies, it can be concluded that the association between PCOS and AIT, specifically HT, is very common. In addition, elevated TSH levels are common findings among patients with PCOS. AIT is more prevalent in women with PCOS than non-carriers; as well as TSH levels are also higher in PCOS patients compared to their respective controls. The main findings of these studies are reported in table 1. The next section will discuss the possible etiological and pathogenic factors for the occurrence of these phenomena.

Table 1: Main findings and their significances in the original studies cited in the review

Original study	Country	Publication Year	Sample	Findings and significances
[3]	China	2016	100 PCOS women vs 100 controls, matched for age and body mass index (BMI).	<p>PCOS women compared with controls:</p> <ul style="list-style-type: none"> - Significant levels of anti-TPO ($p < 0.01$). - Characteristic hypoechogenicity trough US was significantly higher (34% vs 7%, $p < 0.01$). - AIT was more prevalent (25% vs 2%, $p < 0.001$). - Significant levels of TSH ($p < 0.001$). <ul style="list-style-type: none"> - Lower levels of T_3 ($p < 0.001$). - Overt hypothyroidism was 3% vs 0% ($p < 0.01$). <ul style="list-style-type: none"> - SCH was 27% vs 8% ($p = 0.0002$). - Prevalence of euthyroidism was lower (68% vs 91%, $p < 0.0001$).
[10]	Iran	2012	78 PCOS women vs 350 controls, matched for age.	<ul style="list-style-type: none"> - Higher anti-TPO levels in PCOS women ($p = 0.040$). - Anti-TPO positivity did not differ between case and control groups (30.6% vs 27.8%, $p = 0.730$). - TSH levels also did not differ significantly between patients with PCOS and women in the control group (2.77 ± 3.8 IU/mL vs 2.29 ± 1.5 IU/mL, $p = 0.09$).
[12]	Turkey	2015	86 PCOS women vs 60 controls. The subjects under the age of 18 or in the peri-menopause or post-menopause stage were not included in the study.	<ul style="list-style-type: none"> - PCOS patients had significantly higher levels of anti-TPO and anti-Tg when compared to the control group ($p = 0.017$ and $p = 0.014$, respectively). - Anti-TPO levels were positive 26.7% of the PCOS patients compared to 6.6% of the controls ($p = 0.002$). <ul style="list-style-type: none"> - Positivity for anti-Tg was found in 16.2% of the PCOS group vs 5% of the control group ($p = 0.039$). - HT was observed in 22.1% of those with PCOS and it was 5% of the control group ($p = 0.004$). - TSH levels were higher in the PCOS group than in the control group ($p = 0.037$).

[13]	Italy	2013	113 PCOS women vs 100 controls, matched for age.	Higher prevalence of AIT in PCOS patients compared to the group control (27% vs 8%, $p < 0.001$).
[15]	Italy	2015	50 PCOS women. Study performed to investigate the association of AIT and levels of 25 (OH) vitamin D.	AIT was observed in 24% of these patients. 25 (OH) vitamin D levels were significantly lower in AIT patients when compared with patients without AIT (32.0 ± 22.6 vs 49.6 ± 19.9 nmol/L; $p = 0.02$).
[16]	Brazil	2013	168 PCOS women with an age average of 24 years.	SCH was observed in 11.3% of these patients.
[17]	Turkey	2014	73 PCOS women vs 60 controls, matched for age.	AIT in PCOS patients was 32.5% vs 23.3% in the control group, with no statistically significant difference ($p = 0.394$).

PCOS: polycystic ovary syndrome. vs: versus. Anti-TPO: anti-thyroid peroxidase. AIT: autoimmune thyroiditis. TSH: thyroid stimulating hormone. US: ultrasound. T3: triiodothyronine. SCH: Subclinical hypothyroidism. Anti-Tg: Anti-thyroglobulin. HT: Hashimoto's thyroiditis.

Pathogenesis

The exact pathogenic mechanism of polycystic ovary syndrome (PCOS) is still a topic of debate, being considered a heterogeneous disease with genetic and environmental components [15]. Endocrine-metabolic aspects play an important role, such as gonadotropin concentrations [7], of sex hormones [12], and hyperinsulinemia [6]. In addition, the presence of high levels of anti-ovarian antibodies in some women with PCOS suggests a related autoimmune factor [12], although the role of autoimmunity in the pathophysiology of PCOS remains controversial [18]. The etiology of AIT is not fully elucidated and it is considered that the interaction between genetic susceptibility and environmental factors acts as a trigger for the installation and progression of thyroid autoimmunity [12].

In HT is observed a strong genetic predisposition through family and twins. Kowalczyk *et al.* [9], in a review, mention a study in which children and siblings of patients with HT, the risk of developing HT is increased by 32 times and 21 times, respectively, with predominance in women. Gaberšček *et al.* [6] mention that 73% of the susceptibility for the development of thyroid autoantibodies can be attributable to genetic factors based on study carried out with Danish twins. Several genes are known to be associated with the disease onset, progression and severity: human leukocyte antigen (HLA-DR); CD40; cytotoxic T-lymphocyte-associated protein 4 (CTLA4); protein tyrosine phosphatase 22 (PTPN22); interleukin 2 receptor, alpha (IL2RA); vitamin D receptor (VDR); and, the only thyroid specific gene associated with HT, the gene for thyroglobulin (Tg) [6].

In PCOS, familial aggregation is well established [6,9]. Presence of PCOS features has been documented more frequently in first-degree relatives of women with the disease [6,9]. It has been documented several

genes suspected of influencing PCOS development, but the results of research on most of them are inconclusive. Candidate genes are: fibrillin 3 (FBN3); insulin; insulin receptor; insulin receptor substrate 1; transcription factor 7-like 2; calpain 10; fat and obesity associated gene (FTO); sex-hormone-binding globulin (SHBG); and VDR [6]. Lately, in genome-wide association studies (GWAS), was identified the DENNDD1A gene, coding a protein participating in endosomal membrane transport, as a susceptibility gene for PCOS in an Asian population [9].

The pathogenesis of the association between PCOS and AIT is unclear [13] and data regarding etiology, pathogenesis and clinical implications are still scarce [6]. Considering that both PCOS and AIT present familial aggregation and genetic predisposition, the association between these diseases could be genetically determined. Several genes for susceptibility have been proposed as involved in the etiology of both diseases, but to date there is no well-established common genetic basis [6,9,12]. Three genetic polymorphisms could be involved in the pathophysiology of PCOS as well as of HT: FBN3, GnRHR and CYP1B1 [6].

Polymorphisms of FBN3 have influence on activity and levels of transforming growth factor beta (TGF beta) via fibrilins (FBNs). TGF beta acts as a key regulator of immune tolerance by stimulating suppressive Tregs and inhibiting T cell differentiation [6,9]. In hypothyroid HT lower serum levels of TGF beta when compared with healthy controls has been evidenced [6]. Moreover women with PCOS carrying allele 8 of D19S884 in the FBN3 gene have lower levels of TGF beta when compared with allele 8-negative PCOS patients, and, thus, theoretically they are more prone to develop HT. In relation to this, further investigations need to be performed [6,9].

A relationship between the 3'-UTR variant rs1038426 of gonadotropin-releasing hormone receptor (GnRHR) and insulin metabolism in PCOS women as well as an association with thyroid function in those patients is possible. A relation with serum levels of TSH and that genetic variant has been shown [6,9].

The CYP1B1 gene is associated with PCOS and encodes an enzyme that oxidizes estradiol to 4-hydroxiestradiol. Polymorphism CYP1B1 L432V (rs1056836) was related with serum levels of thyroid hormones [6,9].

The potential pathogenic link between PCOS and AIT may involve inflammatory mechanisms [19]. About 50 to 70% of all women with PCOS have some degree of insulin resistance (IR) [20] and this is an important risk factor for the development of type 2 diabetes mellitus. It has been shown that patients with PCOS have high levels of cytokines such as tumor necrosis factor alpha (TNF alpha) and interleukin 6 (IL-6), regardless of the presence of obesity [12,13,19], with PCOS being characterized as a low-grade inflammatory condition [13]. IL-6 is a potential mediator of autoimmunity by T3 lymphocytes. Through IR and an inflammatory environment there may be a reduction in deiodinase-2 activity and thus cause a relative decrease in T3 and an increase in TSH [3].

Probable etiopathogenic mechanisms for the onset of subclinical hypothyroidism (SCH) in patients with PCOS may be associated with elevated BMI and obesity [3]. Approximately 50% of PCOS patients are overweight or obese and many show increased abdominal circumference [21]. It is known that obesity increases the susceptibility to the installation of inflammatory and autoimmune diseases [21]. Adipose

tissue is one of the most important sources of proinflammatory cytokines, as insulin resistance (IR) and hyperinsulinemia are related to the elevation of these cytokines. Thus, in synergism, insulin resistance and obesity in these patients cause an increase in adipocytokines and other inflammatory markers [19]. Another aspect to be considered is that obesity leads to increased levels of leptin, which would stimulate the hypothalamus to increase the secretion of thyrotropin-releasing hormone (TRH). This pathway, together with other mechanisms, could explain the higher incidence of SCH in women with PCOS [3]. In view of the above, the chronic inflammatory environment present in PCOS carriers may be a potential trigger for thyroid autoimmunity.

Vitamin D deficiency has been linked to the pathogenesis of autoimmune thyroid disease and PCOS [9]. It has been shown to have a positive impact on the immune system and is believed to be able to prevent autoimmune diseases. Therefore, vitamin D deficiency may be involved in an increased risk of autoimmunity [9]. Vitamin D exerts its effects through binding at its receptor, which is expressed in a wide variety of tissues, such as lymphocytes, monocytes and dendritic cell [6]. There is an increased prevalence of vitamin D deficiency [25 (OH) vitamin D] in patients with AIT [15]. There is evidence that calcium and vitamin D supplementation may promote the reduction of inflammatory markers and oxidative stress [9]; and that in women with PCOS this supplementation may improve menstrual frequency and metabolic disorders [6], since low 25 (OH) vitamin D level has a negative impact on metabolism, worsening insulin resistance, hyperinsulinemia and hyperandrogenism [9].

There is evidence of high prevalence of PCOS phenotype in adolescents with HT with normal thyroid hormone function. This suggests that the autoimmunity state itself may play an etiopathogenic role in the PCOS phenotype, regardless of the presence of hypothyroidism [12,19]. Histological findings of autoimmune oophoritis have been observed in some patients with PCOS [12,13]. In addition, some well-known autoimmunity markers such as anti-histone antibody, anti-DNA antibody, antinuclear antibody and smooth muscle autoantibody have been reported with high titers in some patients with PCOS [12]. High prevalence of lupus has been observed in women with PCOS. These findings suggest possible autoimmune mechanisms in the pathogenesis of PCOS [10,12,18]. Reinforcing the hypothesis of autoimmune etiopathogenesis in the association between PCOS and AIT, several original studies have demonstrated high levels of positivity of antithyroid autoantibodies such as anti-TPO and anti-Tg in groups of women with PCOS in relation to their respective controls [3,6,12,13,15]. Although the link between PCOS and autoimmune diseases is the subject of many studies, the results are conflicting and the exact role of autoimmunity in this association remains controversial [13,18].

It is known that the thymus plays an important role in the modulation of the immune system [6,9]. The maintenance of self-tolerance and consequently the prevention of autoimmunity is done through two mechanisms. The first is central immune tolerance with the deletion of autoreactive T cells by the thymus during fetal life. The second mechanism is peripheral immune tolerance promoted mainly by regulatory T cells (Tregs), derived from the thymus and from inactive lymphocytes ("naive cells"), which has a suppressive effect on the immune system and thus prevent excessive immune response [6,9]. Through animal models, there is evidence of immunological dysregulation induced by elevated levels of estrogen during the prenatal period, specifically before 10 days of gestation, when the thymus is in the final stage of maturation. It is believed that such elevated levels of estrogen can affect the maturation of the thymus and lead to the

cessation of Tregs production, which may lead to the formation of multiple ovarian cysts, which supports the hypothesis of the autoimmune etiology of PCOS [6]. In addition to estrogens, adrenal steroids such as corticosterone have already been identified in animal models as causing a decrease in the number of thymocytes and the weight of the thymus; and also as factors for the development of ovarian cysts and anovulation [9]. Thus, dysregulations in the fetal thymus could be involved in immunological intolerance and onset of PCOS and AIT in predisposed individuals [6].

The role of sex steroid hormones in the pathogenesis of autoimmune diseases is plausible, since women are significantly more affected by these pathologies than men. Five percent of the world population has autoimmune disease, with 78% being women [6]. The prevalence of HT is 5 to 10 times higher in women than in men, reinforcing the hypothesis that factors involving sex hormones may be involved in the genesis [12]. In addition, the condition of excess estrogen has been related to different autoimmune diseases, considering the higher incidence of these pathologies in women of reproductive age, as well as has been observed in hypogonadal men, who have relatively high levels of estrogens [2]. It is known that abnormalities in sex hormone levels and balance between them are strongly associated with PCOS [12], with a relative predominance of estrogen over progesterone, and this may have an influence on the etiopathogenesis of autoimmune diseases, including HT [22].

The Role of Sexual Hormones

Theoretically, hormones such as follicle stimulating hormone (FSH), luteinizing hormone (LH) and estrogen have a role in the pathogenesis of thyroid disease in women, which is supported by the finding that thyroid diseases are more common in females [5]. Sexual steroids play an important role in the regulation of the immune system [12,19] and estrogen is capable of activating the inflammatory and immune response [19]. Estrogen can stimulate the immune system by increasing the secretion of interleukin 1 (IL-1) in monocytes, IL-6 in lymphocytes, interferon gamma and tumor necrosis factor alpha (TNF-alpha) [12]. In addition, it has been reported that estrogens decrease the activity of suppressor T cells, increase B-cell activity and direct the Th2 immune response and antibody formation [6]. Thus, female susceptibility to autoimmune diseases is probably increased by the stimulatory action of estrogens in the immune system.

On the other hand, supraphysiological doses of estrogens, such as during pregnancy and in use of oral contraceptives, appear to cause immunosuppression [9]. Clinical manifestations of rheumatoid arthritis and multiple sclerosis tend to alleviate during pregnancy, especially in the third trimester, coinciding with higher levels of estrogen and progesterone [9].

In turn, progesterone has an inhibitory effect on the immune system by blocking lymphocyte proliferation, reducing the oxidative burst of monocytes, reducing IL-6 secretion by monocytes, and altering cytokine secretion in cell clones T to favor the production of IL-10 (an inhibitory cytokine) [12]. The decrease in the peripheral production of antibodies and the proliferation of macrophages can also be attributed to the progestagenic action [6,9]. It is known that autoimmune diseases in women predominantly exacerbate during the menarche and early menopause that are characterized by insufficient progesterone production [12].

Androgens are related to the suppression of the immune response [6,12,23] and are involved in the reduction of many elements of the immune system; in the suppressor T cell activity improvement; in improving the Th1 response; and activation of CD8+ T lymphocytes [6]. Nevertheless, androgen levels in women with PCOS, although increased, are still insufficient to counteract the stimulatory mechanisms of high levels of estrogen and to suppress an excessive immune response [6,12,23].

Due to menstrual irregularities and numerous oligoanovulatory cycles, patients with PCOS have low levels of progesterone and normal or increased levels of estrogen [12]. In the study by Arduc *et al.* [12], where the association between the positivity of thyroid autoantibodies and sex hormones in patients with PCOS was evaluated, a positive correlation was observed between anti-TPO levels and estrogen levels and estrogen/progesterone ratio in these patients; no correlation was observed between the presence of antithyroid antibodies and androgens.

Therefore, it is believed that in women with PCOS, the increased estrogen/progesterone ratio for long periods of oligoanovulation and luteal insufficiency may be involved in hyperstimulation of the immune system and, therefore, in the frequent occurrence of AIT in these patients [2,6,12,15,19,23]. Thus, treatment of oligoanovulatory cycles and restoration of normal menstrual cycles may reduce the risk of onset and/or progression of AIT in patients with PCOS [12]. The possible mechanisms related to sexual hormones in the pathophysiology of the association between PCOS and AIT are summarized in table 2.

Table 2: *The role of sexual hormones in the pathophysiology of the association between PCOS and AIT*

References	Possible mechanisms involving sexual hormones
[19]	Estrogen is capable of activating the inflammatory and immune response.
[12]	Estrogen can stimulate the immune system by increasing the inflammatory cytokines secretion as IL-1, IL-6, interferon gamma, TNF-alpha.
[6]	Estrogens decrease the activity of suppressor T cells, increase B-cell activity and direct the immune response and antibody formation.
[12]	Progesterone has an inhibitory effect on the immune system by blocking lymphocyte proliferation, reducing the oxidative burst of monocytes, reducing IL-6 secretion by monocytes, and altering cytokine secretion in cell clones T to favor the production of IL-10 (an inhibitory cytokine).
[6, 9]	Progestagenic action can also promote the decrease in the peripheral production of antibodies and the proliferation of macrophages.
[6, 12, 23]	Androgens are related to the suppression of the immune response. Androgens are involved in the reduction of many elements of the immune system.
[6]	Androgens are involved in improving the Th1 response and activation of CD8+ T lymphocytes.
[12]	Due to long period of oligoanovulation and luteal insufficiency, PCOS patients have low levels of progesterone, increased levels of estrogen and, therefore, an increased estrogen/progesterone ratio.

[2, 6, 12, 15,
19, 23]

The imbalance in the estrogen/progesterone ratio may be involved in hyperstimulation of the immune system and in the higher frequency of AIT in women with PCOS.

PCOS: polycystic ovary syndrome. AIT: autoimmune thyroiditis. IL-1: interleukin 1. IL-6: interleukin 6. TNF-alpha: tumor necrosis factor alpha. IL-10: interleukin 10. Th1: T-helper 1.

Conclusions

The prevalence of AIT, specifically HT, is significantly higher among patients with PCOS than among non-carriers. Due to this strong association, it is recommended to perform screening for antithyroid antibodies and monitoring of thyroid function in the follow-up of PCOS patients. In these patients, the management of the metabolic syndrome allows the control of the chronic inflammatory state that may impact the thyroid function. Treatment of oligoanovulatory cycles may reduce the risk of AIT onset and/or progression by preventing hormonal factors, especially the increased estrogen levels and high estrogen/progesterone ratio, that through stimulation of the immune response would lead to thyroid autoimmunity. However, with regard to the etiology, pathogenesis and clinical consequences of the association between PCOS and AIT, further investigations need to be performed.

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