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Thyroid Pathology in Polycystic Ovary Syndrome

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) represents a complex endocrine pathology characterized by hyperandrogenism, amenorrhea and multiple ovarian cysts. Often the symptoms begin in adolescence and if not discovered and treated in time, the pathology can lead to serious complications, such as infertility or even cancer, but also many other comorbidities, such as diabetes, dyslipidemia and cardiac artery disease. It may also have influence over the secretion of thyroid hormones.

Material and method: As methods, we conducted a search in international databasis such as PubMed and Thompson ISI in order to identify which thyroid pathology is involved by or in intercorrelation with the PCOS and its implications, thus, laying the basis for a descriptive literature review. We used in our research the following keywords: „thyroid function", polycystic ovary syndrome", selecting only up-dated English articles.

Results: Regarding the fact that there is an increase of endocrine pathology, the intercorelation between PCOS and autoimmune thyroiditis (Hashimoto's thyroiditis) has become more acknowledged in literature as sharing a dual path. The way they interconnect has not yet been sufficiently elucidated, but both pathologies have similar common features and elements that link one another very closely. Also, women with PCOS are more likely to have subclinical hypothyroidism than controls, suggesting that PCOS might be a risk factor for subclinical hypothyroidism. There are only a few studies in the current literature that discuss the association between Graves' disease and PCOS, many of them being only case reports. But these allow the hypothesis that there may be an etiopathogenetic link between these two pathologies.

Conclusion: Thyroid dysfunctions, in the form of autoimmune thyroiditis, hypothyroidism, or Graves' disease, are relatively frequently diagnosed in women with polycystic ovary syndrome and for this reason, it is recommended that these patients should undergo a screening of thyroid function, which consists of determining the titer of thyroid hormones, specific serum thyroid autoantibodies and a thyroid ultrasound.

Keywords: Hypothyroidism; Autoimmune Thyroiditis; Graves disease; PCOS

Introduction

PCOS is a common disorder in teenage girls and women at childbearing age [1,2]. Polycystic ovary syndrome (PCOS) was a recently introduced diagnosis in medical practice. In 1990, PCOS was defined for the first time by three criteria: hyperandrogenism, irregular ovulation and absence of other known fertility diagnoses [3].

PCOS represents a common and complex endocrine pathology characterized through clinical signs, such as hyperandrogenia, ovarian dysfunction and multiple ovarian cysts. These findings can be combinated in different ways to form four PCOS phenotypes [4]. It appears that the prevalence of this syndrome is not precisely known, as various studies have determined the prevalence of this syndrome in patients who had various other comorbidities. Thus, Long et al. found that 21% of women with type 2 diabetes mellitus were also diagnosed with PCOS, with this prevalence being higher in women aged 25–40 compared to women under 25 years-old [2]. There are also differences in the prevalence of PCOS by geographic region of residence. Thus, it was identified that high-income countries (from Europe and North America) generally showed higher rates than Asian ones [4]. The true causes of PCOS development still remain unknown. Recent studies consider a very complex mechanism involving aberrant secretion of gonadotropin-releasing hormone (GnRH), that leads to abnormal gonadotropin secretion, hyperandrogenism, ovarian dysfunction, and insulin resistance [5]. Androgen hypersecretion is caused by intrinsic dysfunction of the thecal cells and/or the hypothalamic-pituitary-ovarian axis. In turn, hyperandrogenism causes abnormal GnRH pulsatility and gonadotropin secretion through aberrant negative or positive feedback of progesterone and estrogen. Abnormal gonadotropin secretion causes a high luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, which induces ovarian dysfunction, including androgen hypersecretion [6]. In addition, the high concentration of anti-Müllerian hormone (AMH), which is secreted by pre-/small antral follicles that accumulate in the ovaries of women with PCOS, further exacerbates ovarian dysfunction by having deleterious effects on the follicular microenvironment and/or pulsation GnRH. Hyperandrogenism is further aggravated by hyperinsulinemia, which develops secondary to insulin resistance.

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Hyperinsulinemia causes an increase in androgen secretion by thecal cells and an inhibition of hepatic production of sex hormone-binding globulin, thus increasing the circulating concentration of bioactive free testosterone. It seems also that PCOS has also a genetic component, fiind implicată mai multe gene [7,8].

Exposure to certain environmental factors predisposes people with predisposing genetic factors to develop PCOS. Environmental factors that can influence the development of PCOS include the intrauterine environment during the prenatal period, when the female fetus is exposed to excess androgens, the follicular microenvironment and the unfavorable lifestyle after birth, in the latter case being references to poor diet, concisisting in high-fat and/or high-protein diet [9]. There is a certain link between diabetes and the development of PCOS. A person who has family members with diabetes may be at risk of developing PCOS. Because excess weight and/or obesity affects mainly women [10] and at the same time obesity can promote endocrinological pathology [11], including PCOS, some authors [12] rised the hypothesis that obesity may act as a trigger factor for PCOS. The clinical manifestations of PCOS are both at the menstrual cycle level and at the dermatological level. According to the latest guidelines, due to ovulatory dysfunction, women with PCOS have irregular cycles, then menstrual cycles duration can be less than 21 days or more than 45 days [13]. Due to hyperandrogenism, women with PCOS present hirsutism (excessive thick-hair growth on the face, and other parts of the body), severe acne on the face, chest and upper back, alopecia (loss of hair of the scalp), and weight gain [13-15]. Women with PCOS are likely to have infertility, but also some other health problems, including diabetes, high blood pressure, high low-density lipoprotein cholesterol (LDL-c), lower high-density lipoprotein cholesterol (HDL-c) and sleep disturbances [16]. Often the symptoms begin in adolescence and if not discovered and treated in time, the pathology can lead to serious complications, such as infertility or even cancer, but also to many other comorbidities, such as insulin resistance, type 2 diabetes mellitus, dyslipidemia, obesity and cardiac artery disease [17,18]. Women with PCOS can present pregnancy complications, such as: spontaneous miscarriage, gestational diabetes, hypertension in pregnancy (preeclampsia), preterm birth, fetal growth abnormalities [19]. In PCOS there are also some influences on the thyroid gland. Actual data suggests a possible link between PCOS and the development of thyroid diseases such as nodular goiter, autoimmune thyroiditis, and subclinical hypothyroidism (SCH), but their origin and cause remains yet uncertain. Some authors consider that there are some genetical background that would be responsible for their development in association with PCOS [20]. Our aim is to identify the thyroid gland diseases that can be associated with PCOS as until today there is only few data on this issue.

Materials and Method

As methods, we conducted a complex search in international databasis (PubMed and Thompson ISI) in order to identify which thyroid pathology is involved by or in intercorelation with the PCOS and its implications, thus, laying the basis for a descriptive literature review. We used in our research the following keywords: „thyroid function", „polycystic ovary syndrome", selecting only up-dated English articles.

Results

Interrelation between PCOS and thyroid function abnormalities

Polycystic ovary syndrome (PCOS) and thyroid disease share common symptoms. It must be taken into account that although they are two different diseases, ultimately both are endocrine pathologies. Both diseases affect both metabolic parameters and fertility in women of reproductive age, and the association of both diseases in the same patient makes the treatment much more difficult to manage [21]. Thyroid hormones have important roles in regulating the function of the female reproductive system. Adequate thyroid hormone secretion is essential for a woman of reproductive age to have normal menstrual function, fertility and to maintain pregnancy. Thus, thyroid disorders cause infertility, spontaneous or assisted abortions, and feto-maternal complications mainly as a result of hypothyroidism, but also as a result of possible hyperthyroidism [22]. The studies conducted so far indicated that young patients with PCOS, particularly women, would be at a high risk of developing thyroid abnormalities such as autoimmune thyroiditis, nodular goiter and hypothiroidism.

Autoimmune thyroiditis and PCOS

Autoimmune thyroiditis is considered to be main cause of hypothyroidism in iodine sufficient areas [23]. Hashimoto thyroiditis is the most frequent form of autoimmune thyroiditis. It is characterized by a diffuse goitrous enlargement of the thyroid, the presence of lymphocytic infiltrates in the form of germinal center formation and atrophic follicles in the thyroid parenchima and the presence of thyroid autoantibodies. It is considered that the disease is the result of an immune-mediated process of antibodies [23, 24]. Regarding the fact that there is an increase in these types of endocrine pathology, the interconnexion between PCOS and autoimmune thyroiditis (Hashimoto's thyroiditis) has become more acknowledged in literature as sharing a dual path [24]. The way they interconnect has not yet been sufficiently elucidated, but both pathologies have similar common features and elements that link one another very closely. At the same time, both pathologies have some common ethiological factors, but some others are different [25]. Both diseases have a multifactorial etiopathogenesis. Genetic influence are well documented in both, but there are also common environmental factors [26]. There is some evidence to suggest that both pathologies may have an autoimmune cause as women with PCOS have shown abnormally elevated levels of several antibodies such as anti-histone, anti-double stranded DNA (anti-dsDNA), and anti-nuclear antibodies, which are specific for autoimmune diseases [26].

More and more researchers have come to the conclusion that there could be a reciprocal interaction between PCOS and Hashimoto's thyroiditis and that, in this situation, it becomes important that patients who simultaneously develop both pathologies will have a greater risk of metabolic and reproductive complications, which will be much more severe. Furthermore, when the female-patients, already diagnosed with PCOS, will also develop autoimmune thyroid disease, the response to infertility treatment is more likely to be poor [26].

A recent study found that 22% of adolescent girls diagnosed with PCOS also presented positive anti-TPO titer and an abnormal ultrasound scan of the thyroid gland characteristic for Hashimoto's thyroiditis, but the authors did't find a significant relationship between PCOS and autoimmune thyroiditis [27]. Another study from Argentina in PCOS patients found a five-fold higher prevalence of thyroid pathology such as autoimmune thyroiditis and/or subclinical hypothyroidism in these patients compared to controls [28].

Hypothiroidism and PCOS

Primary hypothyroidism, caused by a deficiency in iodine intake, is characterized by a reduced production of thyroid hormones and is clinically manifested by a poor ability to tolerate cold, fatigue,

constipation, depression and weight gain. The clinical symptoms of hypothyroidism vary in intensity from subclinical forms to severe cases. Polycystic ovaries can be a clinical feature of hypothyroidism, but, on the other hand, in the making the diagnosis of PCOS, hypothyroidism should be excluded in time. The deranged autoimmunity revealed through the presence of adiposity, increased insulin resistance and high leptin, these being present in both disease states could lay at the basis of both PCOS and hypothyroidism [29]. Subclinical hypothyroidism, defined as a high level of thyroid-stimulating hormone (>2.5 mIU/L) [30], in combination with normal T4 and free thyroxine levels and no signs or symptoms of hypothyroidism, is more common than overt hypothyroidism. Although subclinical hypothyroidism is a mild form, it results in anovulatory cycles, sex hormone imbalances, subfertility and negative effects on pregnancy, to which is added an increased metabolic risk of obesity, insulin resistance and hyperlipidemia, manifestations also present in PCOS [31]. Moreover, a meta-analysis including six studies showed that women with PCOS were 2.87 times more likely to have subclinical hypothyroidism than controls, suggesting that PCOS might be a risk factor for subclinical hypothyroidism. Based on the reviewed articles, the authors hypothesized several possible mechanisms for the increased prevalence of subclinical hypothyroidism in PCOS. These assumptions took into account three possibilities, namely: 1). PCOS can cause subclinical hypothyroidism through the obesity and insulin resistance that characterize it; 2). the compromised immune system in PCOS can be the cause for the development of an autoimmune thyroiditis, which in turn becomes a cause of subclinical hypothyroidism; 3). Based on animal experiments, it can be concluded that there is a strong direct interaction between the thyroid and the ovary because it has been determined that luteal cells of mature corpora lutea may be involved in the synthesis of thyroid hormones [31]. There are some recent studies that have shown that a quarter of women with PCOS have subclinical hypothyroidism and this fact has significant implications because this association may be responsible for clinical, biochemical and metabolic changes that have negative outcomes on reproduction and pregnancy [20,32], but at the same time hypothyroidism can worsen insulin resistance and thus worsen PCOS [33].

Graves disease and PCOS

There are only few studies written so far on the association between Graves' disease, an autoimmune thyroid disorder, and PCOS and many of them are only case reports [34,35], but allow the hypothesis that there may be an etiopathogenetic link between these two pathologies. Graves' disease and PCOS have clinical similarities in the form of menstrual disturbances and marked changes in sex hormones. Autoimmunity disorders may represent one of the possible mechanisms of the association of the two pathologies [36]. However, it appears that a young woman with PCOS may rarely develop a thyroid condition characterized by overt or subclinical hyperthyroidism, such as Graves' disease [37].

Conclusion and Recommendations

Thyroid dysfunctions, in the form of autoimmune thyroiditis, hypothyroidism, or Graves' disease, are relatively frequently diagnosed in women with PCOS and for this reason, it is recommended that these patients should undergo a screening of thyroid function, which consists of determining the titer of thyroid hormones, specific serum thyroid autoantibodies and a thyroid ultrasound.

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