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Polycystic ovary syndrome and thyroid disorders: a link to be uncovered

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ABSTRACT — Polycystic ovary syndrome (PCOS) and thyroid diseases are two common disorders in the female population. These conditions seem to be correlated even if the cause is still unknown. They are characterized by overlapped clinical manifestations and risks, including reproducing, and metabolic aspects. Both diseases could cause a reduction in fertility and an increase in insulin and lipid levels. This review is focused on the connection between PCOS and hypothyroidism and their different treatments, such as inositol, oral contraceptive, insulin-sensitizers for one and levothyroxine, selenium, iodine for the other. In PCOS women a high prevalence of subclinical hypothyroidism (SCH) and autoimmune thyroid disease is found. Therefore, different treatments are examined with more attention on efficacy and safety of inositols, as a therapeutic approach for either PCOS and SCH.

KEYWORDS
Polycystic ovary syndrome, Thyroid disorders, Subclinical hypothyroidism, Inositol, Myo-inositol.

INTRODUCTION

Polycystic ovary syndrome (PCOS) represents one of the most common conditions in reproductive aged women, even if it can be manifested in adolescence or during perimenopause. It is considered an important public health issue. Nowadays, it is estimated that 8-13% of women worldwide present PCOS and can raise up to 70% as undiagnosed cases[1]. PCOS is a complicated endocrine disorder characterised by metabolic, endocrine and psychological impairments. Menstrual irregularities, androgen excess and obesity are included in the clinical manifestations of the syndrome. PCOS could be manifested in different phenotypes and this involves an obstacle for a correct interpretation. As example, the metabolic aspects would appear differentiated among the multiple phenotypes of PCOS, identified by Rotterdam criteria[2,3]. Prior to determinate the PCOS syndrome, the exclusion of other diseases and physical changes with similar clinical manifestations becomes essential. Congenital adrenal hyperplasia, Cushing's syndrome and androgen-secreting tumours, and physical changes such as puberty and menopause for the menstrual cycle irregularity may overlap the similar clinical manifestation of PCOS. The diagnosis of PCOS is based on Rotterdam criteria, set out during the consensus workshop group meeting in 2003[4]. The Rotterdam criteria are similar to the criteria analyzed by the Endocrine Society in the United State[5]. Regarding these criteria, PCOS is diagnosed when two of the three following parameters are manifested: oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries. The syndrome shows a high percentage of varieties by ethnicity, with elevated complications and prevalence in high-risk populations, such as Indigenous women[6,7]. This ethnic difference has led to a discrepancy with the Chinese diagnostic criteria. In fact, in this specific population the presence of hyperandrogenism and polycystic ovaries are not enough to detect the syndrome. The Chinese women should manifest oligomenorrhea, amenorrhea or

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irregular uterine bleeding to diagnose PCOS[5]. Evidence correlates PCOS with a high risk of infertility, hyperandrogenism manifestations like hirsutism, acne, seborrhoea and androgenic alopecia[8-11]. Even if insulin resistance (IR) and hyperinsulinemia are not included in the Rotterdam criteria, they are frequent in PCOS. In PCOS women the insulin-mediated glucose uptake is decreased by 35-40%. The risk of IR and hyperinsulinemia is higher in overweight/obese PCOS women than the normal ones. An Italian study shows that in obese PCOS women the IR is 72% compared with 26.3% in normal weight PCOS[9]. Another study confirmed the same result and deepened the connection between IR, pre-diabetes and type 2 diabetes. Furthermore, this link is exacerbates in overweight and obese PCOS women. Particularly, from normal to overweight and obese women the IR prevalence raises from 19.3% to 56.7% and 78.2%, respectively[12]. IR and hyperinsulinemia expose PCOS women to a greater cardiovascular risk, including dyslipidemia, hypertension and obstruction sleep apnea, and type 2 diabetes development[13].

PCOS TREATMENT

To contrast the PCOS syndrome the first step is regaining a correct lifestyle, especially for the overweight/obese women where a very close link exists between obesity and negative reproductive, metabolic and psychological aspects. In PCOS women non-searching for a pregnancy, the most common treatments used are oral contraceptives (OCPs), metformin, anti-obesity and anti-androgens agents[1]. When the androgen clinical manifestations and irregular cycle appear, OCPs is the first approach for PCOS treatment. However, with this treatment an increase of cardiovascular and metabolic risks, weight gain and psychological impairments are often observed[14]. Metformin is the most common insulin sensitizer used for the metabolic aspect. The results of using metformin is a decrease of IR in several tissue like adipose and ovaries[15]. However, Metformin is responsible for various adverse effects, mainly gastrointestinal and its use is off label in many countries[16]. A new interesting approach involves the use of inositols in PCOS women. Nine isomers exist in the inositol's family, with the same formula deriving from cyclohexane. Myo-inositol (Myo-Ins) is the most abundant in nature. It is involved in the synthesis of phosphoinositides (PtdIns), as a precursor. PtdIns is an important regulator in signal transduction pathway. Myo-Ins acts as a second messenger of different hormones, like follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH) and insulin[17]. In clinics, the most effective dosage is 4 g/day mainly splitted twice a day (2X2), and its safety and absence with regards to side effects has been confirmed by different uses in many studies[18]. A recent meta-analysis, involving 247 case and 249 controls, was conducted to evaluate the efficacy of Myo-Ins alone or in combination with D-chiro-inositol (D-chiro-Ins), in their physiological ratio (40:1)[19], on the metabolic parameters of PCOS women. The results obtained are extremely positive and show Myo-Ins as an effective molecule in improving the metabolic and hormone profile of PCOS women[20]. The improvement of the reproductive parameters by Myo-Ins alone or combined are also shown in another recent meta-analysis[21]. Thanks to their safety and efficacy, inositols have had the access to the new ESHRE Guidelines 2018 for the treatment of PCOS[1].

HYPOTHYROIDISM

Hypothyroidism is characterized by a thyroid hormone deficiency. It could be either subclinical (SCH) or overt. SCH is defined as TSH level higher than the upper reference limit, 4 mIU/L, and a normal free-thyroxine level (0.6–1.8 ng/dL)[22]. Frequently SCH is asymptomatic, and for this reason a therapy is not always recommended. However, untreated SCH could develop in overt hypothyroidism[23]. The National Health and Nutrition Survey (NHANES) – the biggest epidemiological research conducted in the USA on a group of 17 000 subjects – shows that the incidence of hypothyroidism in the Eastern women of reproductive age is around 4%, with a higher prevalence given by the SCH. Among young women the most likely thyroid disorder is Hashimoto thyroiditis (HT), which is characterized by elevated level of autoantibodies, such as anti-thyroid peroxidase (TPOAb) and/or anti-thyroglobulin (TgAb), with normal TSH level. The manifestation of HT and SCH is very frequent because the second disease is a consequence of the first. In the USA, an epidemiologic study evaluated the incidence of positive antibodies in different age groups: the group of 20-29 years old showed an incidence of 11.3% TPOAb and 9.2% TgAb, whereas an increased prevalence was observed in the 30-39 years old group (14.2% and 14.5%, for each antibody)[24]. Evidence links hypothyroidism with alterations of several processes in reproduction, metabolism, cardiovascular and bones[25,26]. Thyroid owns a central role in the metabolism pathways. Overt and SCH negatively impact the lipid metabolism, increasing the risk of cholesterolemia and cardiovascular disease[27]. Furthermore, a direct relationship between IR, cholesterol and SCH has been identified[28].

HYPOTHYROIDISM TREATMENT

Over the last 50 years levothyroxine is the main treatment for hypothyroidism[29]. Besides, other

compounds are used effectively as therapy for hypothyroidism patients. Molecules such as Myo-Ins, iodine, selenium and vitamin D seem to be useful in patients with hypothyroidism, SCH and thyroiditis, like HT. In the last years, different studies have reported the use and the efficacy of Myo-Ins in SCH and HT patients. TSH, TPOAb and TgAb levels were significantly decreased after a 6 months supplementation of 600 mg of Myo-Ins in association with selenium, leading to euthyroidism[30-32]. Furthermore, Myo-Ins plus selenium supplementation has proved to be useful also in HT patients only, where there is an improvement on the antibodies levels, reducing the overt hypothyroidism risk[33]. Iodine has a crucial role in the neuronal development. The guidelines recommend the right supplementation of 250 mcg in pregnancy women[34]. The beneficial role of a right iodine supplementation is also documented in management of thyroid nodules. A higher reduction in thyroid benign nodules volume occurred in euthyroid patients treated with iodine alone compared to placebo and with iodine plus levothyroxine respect to levothyroxine alone[35]. Selenium and vitamin D are used in HT, maintaining stable the titer antibodies. Lower level of TPOAb were detect after a levothyroxine plus selenium treatment compared to levothyroxine alone in patients affected by autoimmune hypothyroidism[36]. An inverse relationship between prevalence of autoimmune thyroid diseases (AITDs) and vitamin D are well known, with a lower level of this vitamin in HT[37]. The same negative link was found also with TSH level. Mirhosseini et al[38] have reported an improvement of TSH and TPOAb and TgAb after vitamin D supplementation in deficient patients.

PCOS AND THYROID

In the last years a significant relationship between PCOS and thyroid dysfunction draws attention to researchers and clinicians[39]. Evidences highlights the link between hypothyroidism and female reproduction system. Indeed, in women in fertile age, hypothyroidism impairs the cycle length and can cause oligomenorrhea, amenorrhea, polymenorrhea, as well as menorrhagia. In fact, TH adjusts the stimulatory effects of FSH on follicular growth and apoptosis suppression[40]. Alteration of the reproductive system could be manifested not only in the overt hypothyroidism, but also in SCH. In the ATA Guidelines 2017 for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum, the authors recommend the evaluation of serum TSH in all women looking for pregnancy. They suggest treating all women with SCH undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) in order to achieve a TSH concentration <2.5 mU/L[41]. Numerous studies evidence an alteration of the reproductive system with an abnormal thyroid function. Lower free-triiodothyronine (fT_3) and positive TPOAb are associated with a lower antral follicle count (AFC) in 436 women seeking fertility[40]. The study of Wang et al[42] reported that women with positive TPOAb have a higher endometriosis and PCOS incidence than the negative ones. A significant difference was highlighted also for the rate of PCOS; 43,9% in (+) TPOAb and 21,3% in (-) TPOAb. In the same study Wang et al[42] demonstrated a difference between age group, where the PCOS patients aged 28-35 years old are more influenced by (+) TPOAb. Even if evidence should be increased, also the SCH was involved in infertility and negative pregnancy outcome. Precocious ovarian failure, tubal disturbances and ovulatory dysfunction may be shown in higher prevalence in SCH group respect to thyroid normal infertile patients[43]. Another study observed a greater prevalence of AITDs in PCOS patients[44,45]. Comparing PCOS with non PCOS, the first group presented an increased prevalence of goitre and TPOAb than the other[46]. Similar results were published by Arduc et al[47], where the prevalence of TPOAb in PCOS women was 26.7% *vs.* 6.6% in non PCOS. In the same article the TSH and TgAb levels resulted elevated in PCOS group than the control, with a 26.7% of prevalence of high TSH in PCOS. Other works investigated the PCOS with hypothyroidism, overt and subclinical. one hundred seventy five PCOS women compared with 168 control displayed an increased TSH mean level and a high percentage of women with TSH above the normal range level[48]. Yu et al[49] demonstrated an abnormal thyroid function in PCOS women among 100 patients 3% presented overt hypothyroidism while 27% SCH and 25% AITDs. Moreover, they found also elevated prevalence of goiter (25%). Thyroid function and PCOS influence negatively the metabolic parameters. PCOS plus SCH raised the level of fasting plasma glucose and HOMA index[50]. In a meta-analysis, de Meiros et al[51] analyzed the effect of the two simultaneous diseases on the lipid asset comparison with euthyroid PCOS. Women with PCOS and SCH have altered level of total cholesterol (TC), tri-glyceride (TG) and high-density lipoprotein cholesterol (HDL). In another study also, a low-density lipoprotein cholesterol (LDL) increase was demonstrated in PCOS women associated to SCH women[52]. Moreover, a cohort study of PCOS women treated with thyroid hormonal had higher systolic blood pressure and were obese than euthyroid PCOS[53]. Other evaluations should be done on the different typo of PCOS and SCH. In IR-PCOS women treated with metformin or metformin plus inositol for 6 months showed improvement on the metabolic profile and a decrease of TSH levels, with a very significant difference in the second group[54].

CONCLUSIONS AND FUTURE PROSPECTIVE

Several evidences show the link between PCOS syndrome and thyroid dysfunction, with a high prevalence of cardiometabolic risks associated to these diseases. Recent studies support the efficacy in reducing TSH levels with the use of insulin sensitizers. Scientific data support the beneficial effects of inositols, mainly Myo-Ins, either in PCOS and SCH. However, more investigations should be done to better evaluate this treatment for women affected by the two diseases.

Conflicts of interest:
The Authors declare that there are no conflicts of interest.

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