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Thyroid Dysfunction in Polycystic Ovary Syndrome

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Abstract

Thyroid dysfunction and Polycystic ovary syndrome(PCOS) are the two most common Endocrine disorders in Females. Both endocrine disorders share common predisposing factors and gynecological features and have profound effects on reproductive function in women. In one of the crosssectional studies the prevalence of Thyroid dysfuction in PCOS was found to be around 33% by Rotterdam's criteria. The consequences of subclinical hypothyroidism or thyroid autoimmunity in subjects with PCOS are yet to be understood and its work is still ongoing. Robust data needs to be generated to evaluate the importance of thyroid dysfunction in PCOS females in child bearing age group with focus on fertility. This review article highlights the overall prevalence of thyroid disorders in PCOS, the effects of one disorder over the clinical presentation of the other and the consequences of these endocrinopathies on over all metabolic health and fertility of females.

Keywords: Hypothroidism; Hyperthyroidism; PCOS; Autoimmunity

Abbreviations

PCOS: Polycystic Ovary Syndrome; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; TSH: Thyroid-Stimulating Hormone; FT4: Free Thyroxin; SHBG: Sex Hormone-Binding Globulin; SCH: Subclinical Hypothyroidism; ATA: American Thyroid Association; IVF: In-Vitro Fertilization; ICSI: Intracytoplasmic Sperm Injection; TRH: Thyrotropin-Releasing Hormone; LDL-C: Low-Density Lipoprotein Cholesterol; TPO: Thyroid Peroxidase.

Introduction

Polycystic ovary Syndrome(PCOS) and Thyroid disorders are two common widespread endocrine disorders. Many patients with polycystic ovary syndrome (PCOS) also experience thyroid disorders and high levels of Anti-TPOAb as compared to Non-PCOS women [1,2]. PCOS, the most common endocrine problem in reproductive-age women leads to systemic metabolic manifestations and neuroendocrine-immunity disturbance [2]. PCOS is a diagnosis of exclusion, however, after ruling out thyroid dysfunction or other disorders that mimic PCOS.

It includes hyperandrogenism (HA)/hirsutism, oligo- or amenorrhea, and polycystic ovaries (PCO). PCOS is a heterogeneous disorder resulting in several health issues, including menstrual dysfunction, hirsutism, acne, infertility, obesity, metabolic syndrome, and others including autoimmune disorders.

Approximately 15–20% of women of reproductive age are affected by PCOS. PCOS women are at risk of a range of Endocrinological and metabolic disturbances including infertility, obesity, insulin resistance, and metabolic syndrome. In addition, there is also an increasing body of

evidence that suggests that PCOS is linked to increased prevalence of thyroid dysfunction such as autoimmune thyroiditis and nodular goiter.

The objective of this narrative review is to understand the relationship between these two disorders. Relevant articles from this search were retrieved and incorporated.

Linkage of Polycystic Ovary Syndrome and Thyroid Dysfunction

Common clinical features of PCOS include oligomenorrhea, amenorrhea, infertility, hirsutism, weight gain, central obesity, and acanthosis nigricans. Biochemically, it can have hyperandrogenemia, hyperinsulinemia, elevated Luteinizing hormone(LH), decreased Follicle Stimulating Hormone(FSH) and normal levels of cortisol, prolactin (PRL), thyroid-stimulating hormone (TSH), thyroxine (T4), and free thyroxin (FT4) [2]. Low levels of sex hormone-binding globulin (SHBG) may represent a hyper-insulinemic status. Common metabolic derangements in PCOS include Dyslipidemia, dysglycemia, and insulin resistance, increasing the risks of type II diabetes mellitus and cardiovascular disease.

Primary hypothyroidism is a state of deficient thyroid hormone production by the thyroid gland. Common symptoms are cold intolerance, constipation, tiredness, depression, and weight gain. In addition to playing an important role in regulating metabolism, thyroid hormones also play an important role in reproductive health. TSH receptors are widely expressed in the ovary, uterus, and in the feto-maternal unit during implantation. Thyroid hormone deficiency may affect gonadal function and fertility, resulting in delayed puberty and anovulatory cycles [2]. PCOS and Primary overt hypothyroidism shares many of the signs and symptoms which includes irregular menses, infertility, hyperandrogenic features and gain in weight. Hormonally it is characterized by mild increase in total testosterone (T) and free testosterone (fT) levels, increased total and free estradiol (E2), high LH and PRL, and low SHBG levels. Moreover, ovaries with multi-cystic appearance are frequently found in patients with such thyroid dysfunction. It must be noted that ovaries with multi-cystic appearance can be seen in other conditions including hypothalamic amenorrhea.

Severity of hypothyroidism varies significantly, from transient and subclinical forms to severe cases. In fact, subclinical hypothyroidism (SCH), defined as an elevated TSH level in combination with normal T4 and free thyroxine (FT4) levels and lack of signs or symptoms of hypothyroidism, is more common than overt hypothyroidism. The prevalence of SCH is affected by geographic regions, ethnicity, and age in general population. Although SCH is a mild form, it also results in anovulatory cycles, sex hormone imbalances, subfertility, and adverse pregnancy outcomes, which are also features of women with PCOS.

SCH is associated with body weight gain, sex hormone-binding globulin (SHBG) increase, androstenedione to testosterone conversion increase, and aromatization to estradiol [3]. In addition, patients with SCH have increased metabolic risk of obesity, insulin resistance and hyperlipidemia similarly to those with PCOS [4].

In a cross-sectional study by Novais et al. the prevalence of subclinical hypothyroidism (SCH) in non-pregnant women with PCOS was 16.9% compared to 6.2% in the non-PCOS group. The reported prevalence of SCH in the Indian PCOS population was nearly 22.5% [5].

TSH has been described as the most sensitive parameters for detecting minor degrees of primary thyroid hormone deficiency. But there is a controversy on treatment threshold based on TSH value in infertile women. According to 2017 American thyroid association (ATA) guideline, evidence suggesting TSH 4.0 mU/L instead of 2.5 mU/L as treatment threshold of levothyroxine (L-T4) in women before or in pregnancy. While in those undergoing in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) ATA guideline suggest they treated with L-T4 and goal of treatment is to achieve TSH concentration <2.5 mU/L. That indicating in infertile women, there might has underlying subtle hypothyroidism even in those with normal thyroid function. Although PCOS is the most common cause in women with infertility, rare studies investigate the association of TSH and HA in euthyroid PCOS population.

Two entities of hypothyroidism and polycystic ovary syndrome have many features in common, however they are entirely different based on their etiopathogenesis. In primary hypothyroidism an increase in ovarian volume and cystic changes in ovaries have been reported. It is increasingly realized that thyroid disorders are more common in women with PCOS as compared to the normal population. It is unclear if there are some common factors predisposing a person to both disorders, or existing pathophysiological connection between these two factors.

Both endocrine disorders share common predisposing factors, and gynecological features and have profound effects on reproductive function in women. In a cross-sectional observational study on 100 patients with Poly polycystic ovarian Syndrome based on Rotterdam's criteria, the overall prevalence of thyroid dysfunction was 33% in the study patients with PCOS [6].

Mechanisms for the Increased Prevalence of SCH in PCOS

First, the effect of PCOS on the SCH is likely to be mediated by obesity and insulin resistance. Excessive body weight seems to promote this interplay. In addition, there was no difference in the mean values of all endocrine and metabolic parameters tested in the presence or absence of SCH with PCOS. However, abnormal FPG levels and insulin resistance were more likely in women who had SCH than in women without SCH independently of age and BMI. Second, compromised immune system is likely to be a cause of the interaction between SCH and PCOS since SCH can result from autoimmune thyroiditis. Normally, estrogen's immune stimulatory activity is neutralized by anti-inflammatory actions of progesterone levels [3]. However, progesterone level is near zero in PCOS because of anovulatory cycles. As a result, estrogen overstimulates the immune system, leading to high incidence of autoimmune diseases. Third, the strong direct interaction between thyroid and ovary has been implied by experiments both in humans and animals. For example, thyroglobulin and TSH receptor are detected in bovine luteal cells by immunohistochemistry suggesting that the luteal cells of mature corpora lutea may be involved in the synthesis of thyroid hormones.

Ovaries in Thyroid Disorders

There are multiple pathways well known and established leading to change in ovarian morphology in hypothyroidism. Thyroid disorders may prevent ovulation from occurring at all. In addition, the ovaries are at an increased risk for cyst development if the woman has an underactive thyroid (hypothyroid).

Ovarian morphology may result polycystic in nature in the presence of hypothyroidism.

Rise in thyrotropin-releasing hormone (TRH) observed in primary hypothyroidism advances towards increased both hormones of prolactin and thyroid stimulating hormone (TSH).

The changed ratio of luteinizing hormone and follicle stimulating hormone (FSH) and increased dehydroepiandrosterone from the adrenal gland leads to increased prolactin level resulting polycystic ovarian morphology by inhibiting ovulation [7].

To summarise, hypothyroidism can lead to polycystic morphology of the ovaries. While this morphology can vary with severity and duration of hypothyroidism, there is no evidence to suggest that primary hypothyroidism can lead to PCOS.

Thyroid in Polycystic Ovary Syndrome

The occurrence of subclinical thyroid dysfunction has been assessed as 10%, but in reproductive years this prevalence is considerably low at 4-6% in the general population.

In India, it has been estimated that about 42 million people suffer from thyroid diseases [7]. The study conducted by Deshmukh P Y et al concluded that the prevalence of subclinical hypothyroidism was 18% [8-10].

Various studies described increased rate of thyroid disorders in females with PCOS In recent years. Low-density lipoprotein cholesterol (LDL-C) was observed to be considerably greater in the group of subclinical hypothyroidism [8]. The pathophysiological route linking these two disorders is not clear.

The extremely evident connection is the increased BMI and insulin resistance widespread to both the situations. Increase in BMI is an important part of this condition and is found in a substantial proportion (54-68%) of these cases [9].

There is an interesting association between thyroid functions and obesity but not very clear in term of its pathophysiological mechanisms; there is, however, enough evidence to say that TSH is higher in subjects with high BMI [10-13].

Obesity is linked with different milieu with elevated pro-inflammatory markers and insulin resistance. At pituitary level, associated decreased deiodinase-2 activity results in deficiency of relative T3 level and increased TSH levels [10].

Raised TSH levels, with any of these two pathways, act on adipocytes to increase their proliferation. In culture studies, TSH has been shown to increase proliferation of adipocytes as well as increase in production of pro-inflammatory markers from adipocytes, acting on TSH receptors present on adipocytes.
Among 60 euthyroid subjects a relationship of normal range TSH to either adipose tissue or insulin resistance was investigated. Volume of visceral adipose tissue was observed to be the only predictor of TSH ($P = 0.01$) [11].

In one of the study, metformin therapy was demonstrated to lower TSH in subjects with clinical and subclinical hypothyroidism [12]. But the association between TSH lowering effect of metformin and insulin resistance does not have enough evidence.

A change in the affinity or in the number of TSH receptors; an increase in the central dopaminergic tone and direct effect of metformin on TSH regulation has been proposed as potential explanations [13].

There is increased rate of thyroid associated autoimmunity in PCOS patients.

When compared to controls, thyroid autoimmunity is closely associated in patients of PCOS. Female patients with PCOS have elevated levels of thyroid antibody, higher thyroid volumes and hypoechogenic consistent with thyroiditis [14].

Thyroid peroxidase (TPO) antibodies have been shown to be present in 27% of the patients when compared to 8% in controls [15].

Are we right in saying, therefore that women with PCOS are more predisposed to autoimmune diseases?
There seem to be some theoretical basis for this statement. Hyperestrogenism a common prevalent state in PCOS has been suggested as one of the reason for the existence of increased autoimmune diseases in females.

Estrogen receptors have a proliferative action on B-lymphocytes and estrogen receptors are also present on T-cell as well as macrophages. In fact, there are some reports of increased autoimmunity in PCOS patients towards organs other than thyroid as well [16].

When women with PCOS (N=109) are compared with age-matched healthy controls in one study, there was significant increase in serum levels of antihistone and anti-double-stranded deoxyribonucleic acid antibodies [17].

A multi-directional link seems to be interplayed in the complex group of PCOS, thyroid dysfunction, autoimmunity and adiposity. This relationship has been further complicated by report of linkage between autoimmunity and adiposity.

Leptin pathway is an interesting explanation is being currently proposed via but requires more explanation [18]. Increased leptin, because of increased adiposity, increases TRH secretion from the hypothalamus via Janus activating kinase 2/signal transducer and activator of transcription 3 factor.

Increased TSH again induces proliferation of adipocytes via TSH receptors on adipocytes.

The consequences of subclinical hypothyroidism or thyroid autoimmunity in subjects with PCOS are yet to be understood and its work is still ongoing.

Conclusion

To summarise, the data suggests that subclinical hypothyroidism and autoimmunity is closely associated with clinical symptomatology of PCOS in women, but the exact mechanism based on its pathophysiological pathway are yet to be revealed. Robust data needs to be generated to evaluate the importance of thyroid dysfunction in PCOS females in child bearing age group with focus on fertility.

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