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Original Article

The relationship between thyroiditis and polycystic ovary syndrome: a meta-analysis

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Abstract: Background: The link between AIT and PCOS has been reported on several studies, but it's true pathogenesis is far from being elucidated. In an attempt to provide evidence of the relationship between PCOS and AIT, relevant literature of AIT markers in women with PCOS was reviewed and analyzed. Methods: PubMed, Embase, Medline, Web of Knowledge and the Cochrane trial register were searched with English language restriction for only human beings. Data were collected and analyzed by Revman. Results: A total of 6 studies, involving 726 PCOS patients and 879 controls, were eligible for our meta-analysis. Conculsion: The prevalence of AIT, serum TSH, anti-TPO and anti-Tg positive rate in PCOS patients are all significantly higher than those in control groups, which suggests PCOS may be a kind of autoimmune disease and has close association with AIT. So, It will be helpful to assess thyroid function routinely in patients with PCOS and offer thyroid hormone replacement therapy if necessary.

Keywords: Polycystic ovary syndrome, thyroiditis, atuoimmune diseases, meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is a metabolic syndrome, characterized by anovulation, hyperandrogenism and polycystic ovary. PCOS exists commonly among women at reproductive age with an incidence rate of 6-10% [1]. The clinical manifestation of PCOS includes oligomenorrhea, infertility, acne, hirsutism, fat, and acanthosis nigricans and so on. In addition, these patients may develop with many other related endocrine and metabolic diseases, and have increased risk of suffering endometrial cancer, impaired glucose tolerance, diabetes, and cardiovascular disease [2, 3]. Researches about the pathogenesis of PCOS mainly focus on two interrelated metabolic elements-insulin resistance (IR) and hyperandrogenism [4]. Nevertheless, pathogenesis of PCOS still remains unclear.

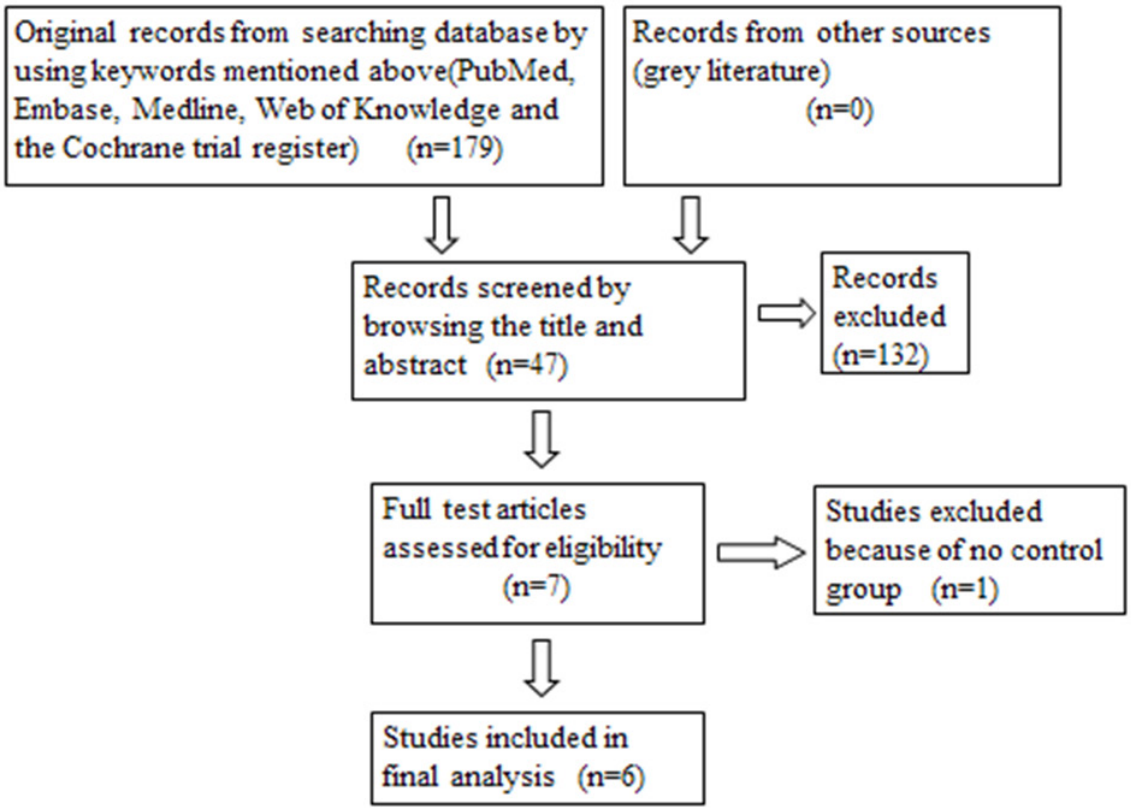
Recently, several researchers suggested the relationship between PCOS and autoimmunity with controversial results, which showed that serologic makers of autoimmunity elevated in patients with PCOS [5]. Gleicher et al. hypothesized that functional autoantibodies could contribute to the development of PCOS, which represents hyperfunction of follicular recruitment in the ovaries, similar to hyperthyroidism in Graves' disease [6]. So, can we regard PCOS as a self-immune disease?

Autoimmune thyroiditis (AIT), or named Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis, is the most prevalent autoimmune state that affects up to 5-20% of women during the age of fertility [7] which is due to chronic inflammation of the thyroid and can lead to hypothyroidism finally. Most of the AIT patients show positivity for anti-TPO and/or anti-Tg and a typical hypoechogenic pattern in ultrasound scan [8, 9]. The link between AIT and PCOS has been reported in several studies, but it's true pathogenesis is far from being elucidated.

The aim of this paper was to assess the relationship between PCOS and thyroiditis.

Search methods

The following electronic databases were searched up to July 2013: PubMed, Embase, Medline, Web of Knowledge and the Cochrane trial register. Search terms included PCOS (polycystic



Picture 1. Search strings of analysis.

ovary syndrome, PCOS, PCO) and "thyroiditis" or "autoimmune thyroiditis" or "autoimmune" or "AIT" or "Hashimoto's thyroiditis" or "thyroid", and researches were limited to only human beings. All articles that could possibly be related to PCOS and thyroiditis were preselected. The search strings were presented in **Picture 1**.

Selection and exclusion criteria

(1) Papers defining PCOS according to either revised 2003 Rotterdam criteria, National Institute of Health (NIH) criteria, or other compatible criteria (Supplementary data) were included in our study. (2) AIT was diagnosed at the base of at least two of the following criteria [10]: (a) TSH levels above the normal range; (b) anti-TPO and/or anti-Tg positivity; (c) Diffuse hypoechogenic pattern with high vascularization by ultrasonography. (3) Studies included must have similar study method. (4) Studies without control groups were excluded, and Studies with subjects enrolled having diseases other than PCOS and thyroid dysfunction, taking any other kind of medicine which could have influence on the test result, or being pregnant were also excluded. (5) Clear data can be extracted from full test of each study and gathered to analysis.

Data collection and analysis

Data were collected and analyzed by Revman 5.0. The effect sizes (ES) for dichotomous variables were odds ratio (OR), for continuous variables were means difference (MD). 95% confidence interval (95% CI) was given for all effect sizes. The level of significance was set at $P<0.05$. Fixed effect model was used when $I^2<50\%$, otherwise, random effect model was used for analysis.

Results

There were 179 potential articles entered our first screen. 132 articles were excluded through browse of the title and abstract because of no close link to our topic. 40 articles were excluded after full test assessed because full data couldn't be extracted, and without control group. Finally, a total of 6 studies [10-15] (**Table 1**), involving 726 PCOS patients and 879 controls, were eligible for our meta-analysis.

Table 1. Characteristics of 6 studies included

Author	Year	Study	PCOS diagnosis criteria	N (PCOS)	N (non-PCOS)	Country
Garelli	2013	case–control	Rotterdam	113	100	Italian
Sinha	2013	case-control	Rotterdam	80	80	India
Kachuei	2012	case–control	Rotterdam	78	350	Iran
Janssen	2004	prospective-cohort	amenorrhea, hyperandrogenism	175	168	German
Anaforoglu	2011	case–control	Rotterdam	84	81	Turkey
Ott	2010	retrospective cohort	ESHRE/ESGE	196	100	Austria

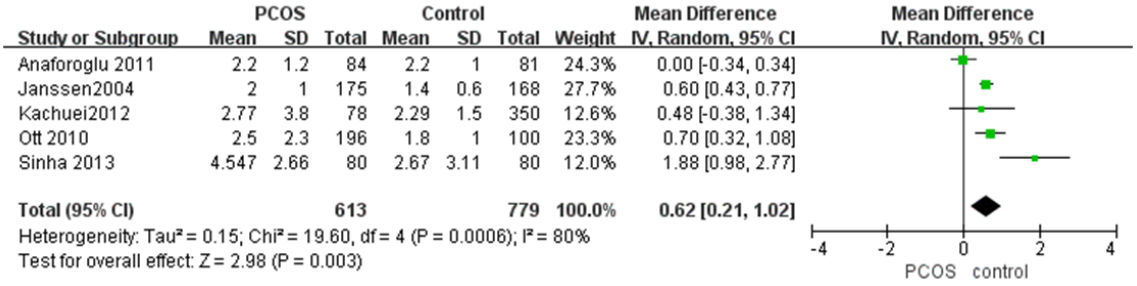


Figure 1. Forest plot of TSH in PCOS patients vs non-PCOS patients.

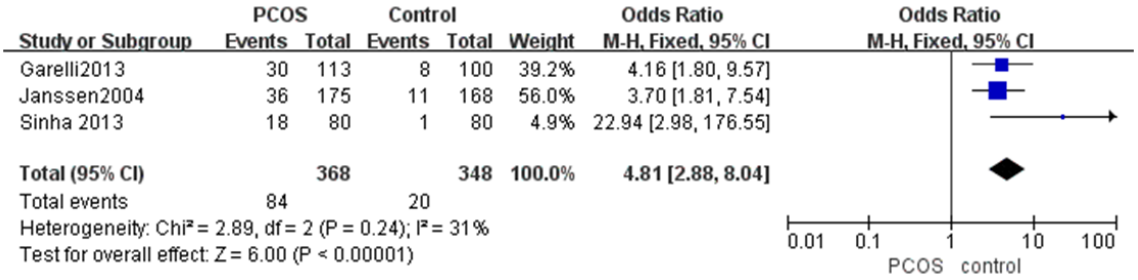


Figure 2. Forest plot of prevalence of AIT in PCOS patients vs non-PCOS patients.

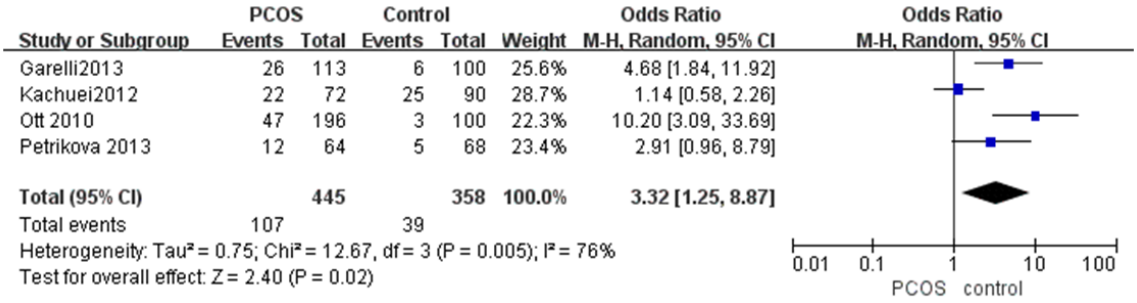


Figure 3. Forest plot of Anti-TPO positive rate in PCOS patients vs non-PCOS patients.

Thyroid stimulating hormone (TSH)

TSH was tested in 5 of the 6 included studies, data were all extracted as means ± standard deviation, the *P* value of heterogeneity between studies was with significant (P=0.0006<0.05, **Figure 1**), so we used the random effect model (random effects MD (95% CI)=0.62, [0.21, 1.02]), and test for overall effect was with significance (P=0.003). The effect size revealed that the TSH level was higher in PCOS patients than in non-PCOS patients.

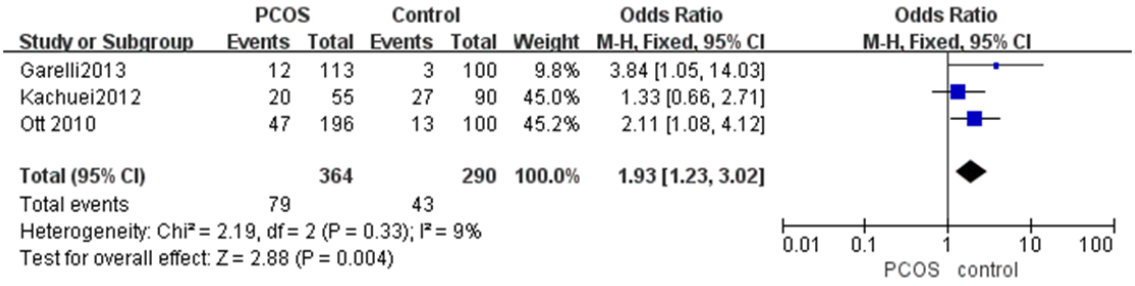


Figure 4. Forest plot of Anti-Tg positive rate in PCOS patients vs non-PCOS patients.

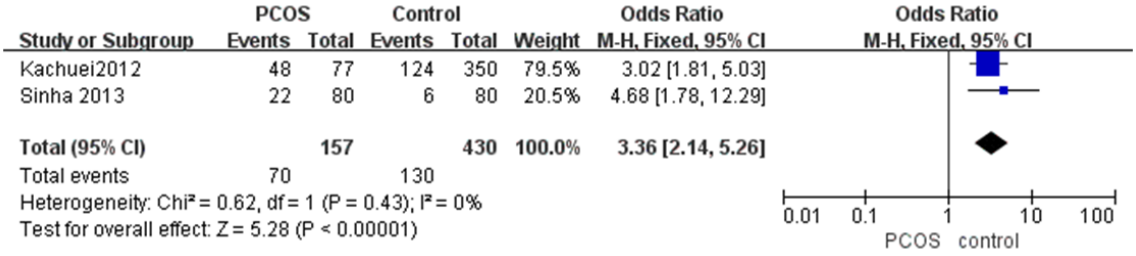


Figure 5. Forest plot of prevalence of Goiter in PCOS patients vs non-PCOS patients.

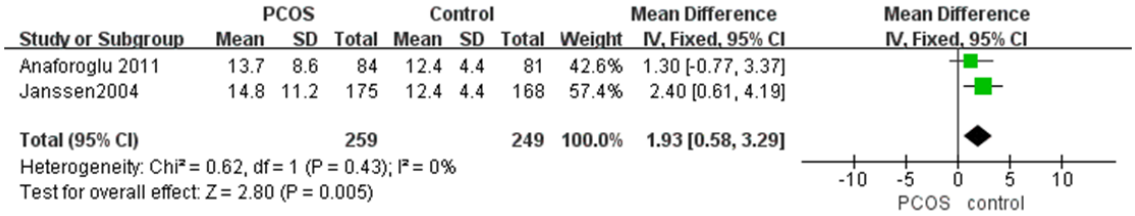


Figure 6. Forest plot of thyroid volume in PCOS patients vs non-PCOS patients.

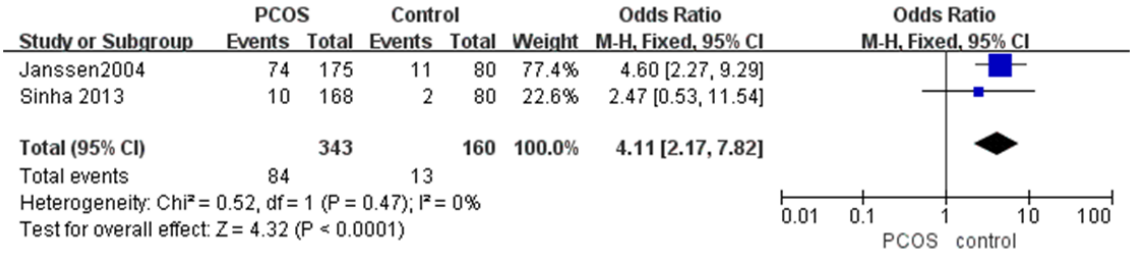


Figure 7. Forest plot of the hypoechoic ultrasound pattern of thyroid in PCOS patients vs non-PCOS patients.

AIT

3 of 6 studies included reported patients with AIT in PCOS and the control groups, the effect size was calculated as OR. The heterogeneity test between studies was with no significant (P=0.24>0.05, **Figure 2**), so we used the fixed effect model (fixed effects OR (95% CI)=4.81, [2.88, 8.04]), test for overall effect was with significance (P<0.00001). The effect size suggested an elevated incidence of AIT in PCOS patients than in controls.

Anti-TPO

4 of 6 studies included reported anti-TPO in PCOS and the control groups, the effect size was calculated as OR. The heterogeneity test

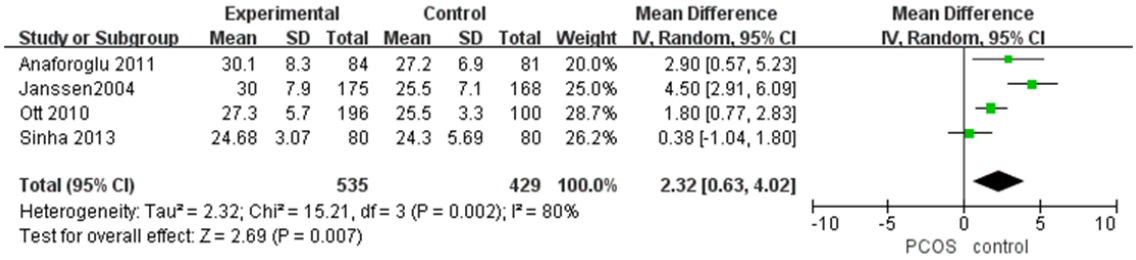


Figure 8. Forest plot of BMI in PCOS patients vs non-PCOS patients.

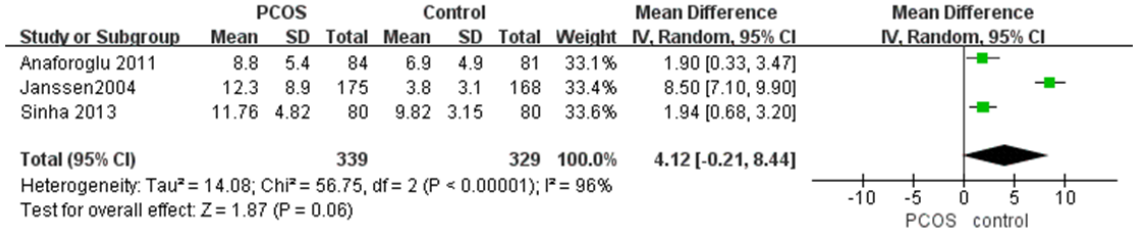


Figure 9. Forest plot of LH in PCOS patients vs non-PCOS patients.

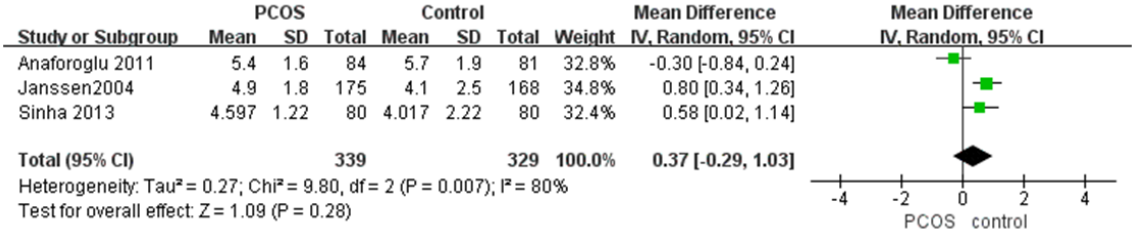


Figure 10. Forest plot of FSH in PCOS patients vs non-PCOS patients.

between studies is with significant (P=0.005-<0.05, **Figure 3**), so random effect model (random effects OR (95% CI)=3.32, [1.25, 8.87]) was used, and test for overall eff-ect was with significance (P=0.02<0.05). The effect size showed that the possibility of anti-TPO positive was higher in patients with PCOS.

Anti-Tg

3 of 6 studies included had data of anti-Tg in PCOS and the control groups, the effect size was calculated as OR. The heterogeneity test between studies was with no significant (P=0.33>0.5, **Figure 4**), so fixed effect model (fixed effects OR (95% CI)=1.93, [1.23, 3.02]) was used, and test for overall effect was with significance (P=0.04<0.05). The effect size showed that the possibility of anti-Tg positive was higher in patients with PCOS.

Goiter

2 studies reported the number of patients with thyroid goiter observed by ultrasonography. The heterogeneity test between studies was with no significant (P=0.43>0.5, **Figure 5**), so fixed effect model (fixed effects OR (95% CI)=3.36, [2.14, 5.26]) was used, and test for overall effect was with significance (P<0.00001), which showed that the prevalence of goiter was higher in PCOS patients.

Thyroid volume

Thyroid volume was calculated in 2 studies, data were all extracted as means ± standard deviation, the heterogeneity test between studies was with no significance (P=0.043>0.05, **Figure 6**), so we used the fixed effect model (fixed effects MD (95% CI)=1.93, [0.58, 3.29]), and test for overall effect was with significance

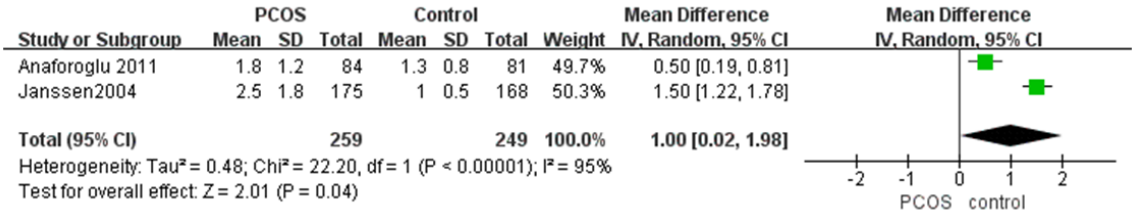


Figure 11. Forest plot of LH-FSH ratio in PCOS patients vs non-PCOS patients.

(P=0.005). Thyroid volume of patients with PCOS was larger than that of control group.

The hypoechoic ultrasound pattern of thyroid

The representative hypoechoic ultrasound pattern related to AIT was reported in 2 studies. The heterogeneity test between studies was with no significance (P=0.49>0.05, **Figure 7**), so fixed effect model (fixed effects OR (95% CI)=4.11, [2.17, 7.86]) was used, and test for overall effect was with significance (P<0.0001). The result implied that maybe some of the subjects do not fulfill the diagnostic criteria of AIT, but this kind of typical ultrasound pattern seemed to be more common in PCOS patients and those patients having the potential to develop into AIT.

Body mass index (BMI)

4 studies calculated BMI, a tool used to assess one's weight status based on the height. The heterogeneity test between studies was with significance (P=0.002<0.05, **Figure 8**), so random effect model (fixed effects MD (95% CI)= 2.32, [0.63, 4.02] was used, and test for overall effect was with significance (P=0.007). Generally speaking , PCOS patients are easier to suffer from overweight or fat than healthy controls, which is in accordance with our result.

LH, FSH and LH-FSH ratio

LH, FSH and LH-FSH ratio was presented in 3, 3 and 2 studies respectively, the difference of LH and FSH was not significant between PCOS patients and control groups (**Figures 9** and **10**), otherwise, the LH-FSH ratio was found higher in patients with PCOS(random effect model , random effects MD (95% CI)=1.00, [0.02, 1.98], p=0.04, **Figure 11**). In Janssen's [11] study, it was found that LH-to-FSH-ratio was higher in thyroid antibody-positive patients, and had some degree of obesity as the controls, which may suggest the potential link between the two parameters, but regretfully, we did not get enough data to do further analysis.

Beside all these indicators calculated above, comparison were also achieved between two subgroups of PCOS patients (with and without AIT) in Garelli's [10] study, and no significant differences were found in terms of clinical features or hormone levels except for TSH. In Ott [12]'s study, there was a general trend towards higher anti-TPO levels in in clomiphene citrate (CC)-resistant women and anti-TPO showed a good predictive value of predicting CC resistance with sensitivity, specificity, positive and negative predictive values of 97.4%, 20.2%, 38.3%, and 93.9% respectively. There was few researches focused on correlations of different reproductive endocrine hormones, antithyroid antibodies or thyroid ultrasound pattern, which may give us more clues on pathogenesis of PCOS and thyroiditis, and may direct to further research and treatment.

Discussion

Thyroid disorders, involving hyperthyroidism and hypothyroidism, can interact with the ovaries through both a direct effect on ovarian function and autoimmunity pathways [16]. AIT, with a prevalence varying from 5 to 15%, 5 to 10-fold common in women than men, which might be explained by genetic factors, the effects of oestrogens and perhaps chromosome X abnormalities, represents the most common endocrine disorders in women at reproductive age. In addition, what makes AIT often ignored is that it may be present without thyroid dysfunction for many years [17] and result in hypothyroidism at last. Nevertheless, interpretation of available data is difficult for a variety of reasons. Heterogeneity of women samples included, different design methods of many studies, small sample sizes, criteria to diagnose AIT and PCOS, ethnic origins and geo-

graphical locations, variable iodine nutrition levels in the populations studied, and other factors may have unpredictable effect on the final results [18, 19].

Although there seems to be no correlations between the underlying causes of hypothyroidism and PCOS, these two diseases have many characteristics in common, such as chronic anovulation; decreased serum sex hormone binding globulin; increased serum testosterone, luteinizing hormone (LH) and cholesterol [20].

Furthermore, a strong interaction between thyroid and ovary is implied by many in vitro researches, both in humans and animals. For example, thyroglobulin (TBG) and TSH receptor are detected in bovine luteal cells by immunohistochemistry [21]. As human chorionic gonadotropin (hCG) has a thyroid stimulating hormone (TSH)-like effect [22], thyroid activity affects the functionality of the reproductive axis [23] and TSH has been reported highly elevated in ovarian hyperstimulation syndrome (OHSS) [24] and PCOS patients.

Genetically speaking, familial occurrence, hereditary factors can be seen in both PCOS and thyroiditis. Nowadays, researches have gone extensively into the molecular genetic level [25]. One study shows that the 3'-untranslated region variant in Gonadotropin-releasing hormone receptor (GNRHR) is associated with serum TSH concentration, insulin levels after oral glucose tolerance test (OGTT) and insulin sensitivity index, which suggest the genetic variant of GNRHR contribute to the phenotypic expression of PCOS. The findings suggest TSH secretion is associated by the loci located in GNRHR [26]. Another research about the functional polymorphism CYP1B1 (which encodes an estrogen enzyme that oxidizes 17β-estradiol to 4-hydroxyestradiol) is associated with serum T4, FT3, FT4, implies that CYP1B1 contributes to the PCOS phenotype expression [27].

As for the immune mechanism, the presence of autoantibodies is one of the classic features of autoimmune diseases [28]. The human ovary, as well as other organs, can be under an autoimmune attack in various circumstances, including several organ-specific or systemic autoimmune diseases. Clinically, the ovarian dysfunction often results in premature ovarian failure (POF), but other diseases, such as infertility, PCOS and endometriosis have also been associated with anti-ovarian autoimmunity [29]. Histopathological features of autoimmune oophoritis with a cystic aspect associated with anti-ovarian serum antibodies have been reported [30, 31]. There are two kinds of autoantibodies, Non-organ specific autoantibodies which are considered abnormal only when they reach a certain high concentrations and organ-specific autoantibodies which react only with specific organs [32]. The search for these antibodies has been undertaken by several researchers with controversial results for anti-ovarian antibodies were detected in the serum of about fifty percent PCOS patients [33] but these results could not be confirmed by others. These different results might be explained by different understanding of potential immune targets, and the methods used for their investigation [34].

The ovary and thyroid are both characterized by two pathologic conditions at the extremes of glandular function: at the hyper-function level, it is PCOS vs hyperthyroidism and in terms of hypo-function, it is premature ovarian failure vs hypothyroidism [35]. Both conditions are being related to infertility, result in abnormal pregnancy outcome and may have an underlying autoimmune etiology [6], we hypothesis that they may be under the control of similar autoantibodies.

Some other researches bring about the hypothesis that the excess estrogens in circulatory system can be linked to many kinds of autoimmune diseases, and the imbalance of estrogen and progesterone may contributes to the prevalence of AIT. In women with normal menstrual period, estrogen could increase the expression of IL-6 in T cells, which has a negative correlation with progesterone [36]. A kind of low-grade inflammatory state in PCOS patients has been demonstrated which characterized by increased levels of circulating C-reactive protein (CRP) [37]. In healthy women, the influence of estrogens on the immune system can be inhibited by progesterone after ovulation, but the absence of this kind of inhibition in patients with PCOS would lead to over-stimulated immune system [38].

Interestingly, on the other part, Ghosh et al summarized the possible pathophysiologic mechanisms of ovarian cyst formation in patients with subclinical and overt hypothyroid-

ism is similar to those occurring in polycystic ovary syndrome [39]. In another study, basal ovarian size of patients with hypothyroidism (with or without polycystic ovaries) was significantly larger when compared with controls. Hypothyroidism was found to produce ovarian cysts, and the polycystic appearance of the ovaries disappeared in all patients after thyroxine treatment. These findings further suggest that the PCOS-like appearance of the ovaries can be caused by primary hypothyroidism [20]. A decrease in ovarian volume, resolution of ovarian cysts and reversal of the polycystic ovary syndrome-like appearance, together with improvement in serum hormone levels, occurred after euthyroidism was achieved [20]. This is also confirmed in a case report of massive ovarian enlargement in women with primary hypothyroidism who received marked clinical improvement, had normal menstruation within 4 months and the ovarian cysts gradually regressed within 6 months treatment with levothyroxine. The phenomenon that serum prolactin level was diminished too leads to the awareness that ovarian and pituitary enlargement may be associated with severe hypothyroidism which could be managed successfully without dangerous and unnecessary operative intervention for ovarian cysts or pituitary adenoma [24]. And the same thing was also observed in children with untreated primary hypothyroidism [40].

One important mechanism of PCOS is insulin resistance. There is a relationship between thyroid function and insulin sensitivity, alterations in lipids and metabolic parameters. In Dittrich's study, women with thyroid-stimulating hormone >or=2.5 mIU/l had a significantly higher body mass index, higher fasting insulin concentrations and altered insulin resistance indices, higher total testosterone, free androgen indices and decreased sex hormone-binding globulin concentrations in comparison with women with thyroid-stimulating hormone <2.5 mIU/l [41] which suggested a threshold of TSH in predicting IR in PCOS patients.

Metformin, an insulin sensitizer agent, results in a significant fall of TSH in obese PCOS patients with hypothyroidism [42] Rotondi [43] confirmed this point later and no such effect was observed in euthyroid patients with PCOS. In another study, Mueller implied that TSH cutoff value around 2 mIU/l had the best sensitivity and specificity for identifying women with IR. And the effect of TSH on IR was independent of age or BMI [44].

In conclusion, although the cause-effect relationship between PCOS and thyroiditis remains unknown, researchers have found out that the prevalence of AIT, serum TSH, anti-TPO and anti-Tg positive rate in PCOS patients are all significantly higher than those in control groups, which suggests PCOS may be a kind of autoimmune disease and has close association with AIT. So, It will be helpful to assess thyroid function routinely in patients with PCOS and offer thyroid hormone replacement therapy if necessary.

Acknowledgements

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Disclosure of conflict of interest

None.

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