Dehydroepiandrosterone Sulfate Level is Lower in Polycystic Ovary Syndrome Patients with Autoimmune Thyroid Disease

Otoimmün Tiroid Hastalığı Olan Polikistik Over Sendromu Hastalarında Dehidroepiandrosteron Sülfat Düzeyi Daha Düşüktür

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ABSTRACT Objective: Polycystic ovary syndrome (PCOS) and autoimmune thyroid disease (AITD) are common endocrinopathies in women. Dehydroepiandrosterone sulfate (DHEAS) level has been found to be low in some autoimmune diseases. In this study, we aimed to evaluate DHEAS level in PCOS patients with AITD compared to control group and relation between DHEAS and thyroid antibody titers. **Material and Methods:** The study population consisted of 59 patients defined as having PCOS and 28 control subjects. We evaluated biochemical and hormonal parameters as well as thyroid parenchyma in PCOS patients and controls. **Results:** The TSH, fT4, DHEAS levels did not differ between the PCOS patients and controls (TSH: 1.9 μIU/mL vs. 1.8 μIU/mL; fT4: 1.0 ng/dL vs. 1.0 ng/dL; DHEAS: 326 μg/dL vs. 316 μg/dL, p>0.05). Serum anti-TPO Ab and anti-Tg Ab levels were significantly higher in the PCOS group. A statistically significant negative relationship was observed between DHEAS and anti-TPO Ab levels (r:-0.356, p=0.004). DHEAS level was significantly lower in anti-TPO Ab positive PCOS patients (204.7 μg/dL vs. 349.4 μg/dL, p=0.009). **Conclusion:** According to our study, we found DHEAS levels were lower in anti-TPO Ab positive PCOS patients than negatives. In accordance with literature, AITD was more prevalent in PCOS patients. We can explain this low DHEAS levels in some PCOS patients with autoimmunity.

Key Words: Polycystic ovary syndrome; autoimmunity; dehydroepiandrosterone sulfate

ÖZET Amaç: Polikistik over sendromu (PKOS) ve otoimmün tiroid hastalıkları (OİTH) kadınlarda sık görülen endokrin hastalıklardır. Dehidroepiandrosteron sulfat (DHEAS) düzeyi bazı otoimmün hastalıklarda daha düşük saptanmıştır. Bu çalışmada, OİTH'ı olan PKOS'lu hastalarda DHEAS düzeyini kontrol grubu ile karşılaştırmayı ve DHEAS ile tiroid antikor titresi arasındaki ilişkiyi değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Çalışma grubu, 59 PKOS tanısı konulan hasta ile kontrol grubu olarak 28 sağlıklı kadından oluşmaktadır. Her iki grubun biyokimyasal ve hormonal parametreleri, ultrasonografi ile tiroid parankimleri değerlendirildi. **Bulgular:** TSH, ST4, DHEAS düzeyleri PKOS hastaları ile kontrol grubunda farklı değildi (TSH: 1.9 μIU/mL vs. 1.8 μIU/mL; fT4: 1,0 ng/dL vs. 1,0 ng/dL; DHEAS: 326 μg/dL vs. 316 μg/dL, p>0,05). Serum anti-TPO ve anti-Tg antikor düzeyleri PKOS grubunda belirgin yüksekti. İstatistiksel olarak anti-TPO antikor ile DHEAS düzeyi arasında negatif ilişki saptandı (r:-0,356, p=0,004). DHEAS düzeyi anti-TPO pozitif PKOS hastalarında belirgin düşüktü (204,7 μg/dL vs. 349,4 μg/dL, p=0,009). **Sonuç:** Çalışmamıza göre, DHEAS düzeyini anti-TPO pozitif olan PKOS hastalarında negatiflere göre daha düşük bulduk. Literatürle uyumlu olarak, PKOS hastalarında OİTH daha sıktı. Bu sonuç, PKOS hastalarında saptanan daha düşük DHEAS düzeyininin otoimmünite ile açıklanabileceğini düşündürmektedir.

Anahtar Kelimeler: Polikistik over sendromu; otoimmünite; dehidroepiandrosteron sülfat

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Polycystic ovary syndrome (PCOS) and autoimmune thyroid disease (AITD) have been known to be the most prevalent diseases in women. PCOS affects at least 5 to 10% of women of reproductive age

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and characterized by laboratory and/or clinical features consisting of hyperandrogenism with chronic anovulation.[1,2] PCOS is associated with a variety of endocrine and metabolic disturbances and increased risk of cardiovascular disease.[3,4] Although there have been conflicting results about the association of PCOS with some autoimmune diseases (with high autoantibodies such as anti-histone, anti-dsDNA, anti-nuclear and anti-smooth muscle cell),[5-8] autoimmune thyroiditis has been demonstrated high among PCOS. Several studies have reported that PCOS patients have increased anti-thyroid peroxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (anti-Tg Ab).[9-12]

AITD is relatively common, ranging from 4 to 21% depending on age, organ-specific autoimmune disorder that can lead to hypothyroidism.[13] Some clinical manifestations of hypothyroidism might be similar to PCOS, so to diagnose PCOS, it is important to exclude hypothyroidism.[2,14,15]

It has recently been demonstrated that serum levels of sulfated DHEAS were low in hypothyroid patients due to AITD and in several other autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis.[16,17] Due to its regulating effect on human immunity, DHEA has been suggested as a possible treatment option for autoimmune diseases.[17,18]

In a recent study, DHEA was used to decrease serum anti-TPO and anti-Tg antibodies in women with premature ovarian failure (POF) and Hashimoto's thyroiditis (HT).[19] Since we have known the association between AITD and PCOS, the aim of our study was to evaluate DHEAS levels in PCOS patients with AITD compared to control group and relation between DHEAS and thyroid antibody titers.

MATERIAL AND METHODS

SUBJECTS

We enrolled fifty nine patients defined as having PCOS according to the revised 2003 Rotterdam criteria and twenty eight age- and BMI-matched subjects who didn't have known endocrinological diseases as the control group.[2] The patients were between 16 and 36 years old and hadn't been pregnant yet. The study was approved by Baskent University Institutional Review Board and Ethics Committee (Project no: KA14/236) and supported by Baskent University Research Fund. All participants gave a written informed consent. This was a case-control study conducted in a university hospital at Endocrinology and Metabolic Diseases clinic.

PCOS was diagnosed according to the presence of two of the three Rotterdam criteria.[2] Clinical hyperandrogenism was defined as hirsutism (Ferriman-Gallwey score ≥8) and/or acne, and/or androgenic alopecia. Biochemical hyperandrogenemia was defined by elevated serum total testosterone (TT), and/or sulfated dehydroepiandrosterone (DHEAS) (>0.82 ng/mL and 430 μg/dL, respectively). Oligomenorrhea was defined as an interval between the menstrual cycles which was ≥35 days and amenorrhea was identified by the absence of menstruation for 6 months or more. Polycystic ovaries (PCO) were diagnosed by transabdominal ultrasound scan when 12 or more follicles in one or both ovaries measuring 2-9 mm in diameter were present and/or when there was an increase of ovarian volume >10 mL. Other causes of hyperandrogenism were excluded by the measurement of prolactin, adrenocorticotropin-stimulated 17-OH progesterone, and the dexamethasone suppression test. Patients with known thyroid dysfunction and taking medication during the previous 3 months, including oral contraceptive pills, steroids and drugs that affect insulin sensitivity were excluded from the study.

The body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2). The anthropometric measurements were taken in light clothing without shoes in the morning after at least 8 hour fasting. The waist circumference was measured at the narrowest level between the costal margin and iliac crest.

Thyroid was evaluated using a high-resolution sonography (General Electric® Loqic P5, USA) with a 12 MHz high-frequency linear transducer. The autoimmune thyroiditis was considered when

thyroid parenchyma was heterogenous and high serum thyroid autoantibodies (anti-Tg Ab and anti-TPO Ab) were detected. According to the normal reference range of the test (0.27≤ thyroid stimulating hormone (TSH) <4.2 μIU/mL), subclinical hypothyroidism (SCH) was defined as serum TSH levels above 4.2 μIU/mL with normal free thyroxine (fT4) levels.

The BMI, waist cimcumference, hirsutism scores were assessed and thyroid sonography was done by the same investigator for all of the subjects.

BIOCHEMICAL EVALUATION

Fasting blood samples were taken after 12-hour overnight fasting at 08:00 am in the follicular phase of a spontaneous or progesterone-induced menstrual cycle. The concentrations of triglyceride (Tg), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and total cholesterol (Total-C) were determined by enzymatic assays (Architect C8000, Abbott diagnostic, USA). The levels of serum hormones including follicle stimulating hormone (FSH), luteinizing hormone (LH), TT, DHEAS, prolactin and fT4, TSH, anti-TPO Ab and anti-Tg Ab were detected with a chemiluminescent immunassay method (Architect i1000 and Architect i2000 system Abbott, USA, respectively). HOMA-IR was calculated as fasting insulin (U/L)×fasting glucose (mg/dL)/405, as described by Matthews et al.[20] The cut-off value was taken as 2.5 for HOMA-IR.

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS software version 20.0. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using medians with interquarter ratio since the variables were non-normally distributed. The Mann-Whitney U test was used to compare variables between the groups. Spearman rho correlations were used to determine associations between the variables. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Clinical, biochemical and hormonal parameters that were found in patients with PCOS and in the control subjects are shown respectively in Table 1 and 2. We recruited 59 patients with PCOS (median age 25, range 16-36 years old; BMI, 27.1 kg/m^2) and 28 age- and BMI-matched control subjects (median age 23, range 17-35 years; BMI, 28.2 kg/m^2). Nineteen of 59 (32.2%) PCOS patients had BMI <25 kg/m^2, forty of them (67.8%) had BMI >25 kg/m^2 of whom half were obese.

TABLE 1: Clinical features and laboratory results of PCOS patients and controls.

	PCOS (n=59)	Control (n=28)	p
Age (year)	25 (16-36)	23 (17-35)	NS
F-G score	10 (0-36)	7 (0-21)	NS
Waist (cm)	91 (72-128)	97 (75-133)	NS
BMI (kg/m^2)	27.1 (18.3-43.7)	28.2 (19.1-40.5)	NS
Glucose (mg/dL)	87 (75-109)	89.5 (76-99)	NS
HOMA-IR	2.4 (0.7-19.4)	2.1 (0.7-10.6)	NS
Total-C (mg/dL)	188.4 (123-280)	174.4 (131-244.8)	NS
HDL-C (mg/dL)	48.5 (30-80)	53.5 (32-64)	NS
LDL-C (mg/dL)	121 (62-196)	102.5 (76-180)	NS
Tg (mg/dL)	104.5 (41-408)	75 (46-164)	NS

F-G: Ferriman-Gallwey; BMI: Body mass index; HOMA-IR: Homeostasis model assessment of insulin resistance; Total-C: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; Tg: Triglyceride.
NS: Not significant.

TABLE 2: The hormonal values of PCOS patients and controls.

	PCOS (n=59)	Control (n=28)	p
fT4 (ng/dL)	1 (0.7-1.3)	1 (0.7-1.2)	NS
TSH (μIU/mL)	1.9 (0.2-8.7)	1.8 (1.1-7.8)	NS
Anti-TPO Ab (IU/mL)	0.6 (0-1020)	0.2 (0-298)	**0.02**
Anti-Tg Ab (IU/mL)	2.6 (0.4-821.2)	1.5 (0.5-15.8)	**0.03**
LH (μU/mL)	5.6 (0.6-17.9)	3.4 (1.1-21)	**0.004**
FSH (μU/mL)	3.9 (1.9-8.2)	4.1 (0.7-6)	NS
Estradiol (pg/mL)	42 (21-132)	32.5 (15-102)	**0.01**
Ttest (ng/mL)	0.6 (0.1-1.4)	0.5 (0.1-0.8)	**0.006**
DHEAS (μg/dL)	325.9 (130.2-880)	318 (145.9-422)	NS
Androstenedion (ng/mL)	2.9 (0.9-11.9)	1.9 (0.9-3.7)	**0.01**

fT4: Free thyroxine; TSH: Thyroid stimulating hormone; anti-TPO Ab: Anti-thyroid peroxidase antibody; anti-Tg Ab: Antithyroglobulin antibody; LH: Luteinizing hormone; FSH: Follicule stimulating hormone; Ttest: Total testosterone; DHEAS: Dehydroepiandrosterone sulfate.
NS: Not significant.

Serum median TT levels in the PCOS patients and the control group were 0.6 ng/mL and 0.5 ng/mL respectively and statistically significant (p =0.006), DHEAS levels were 325.9 μg/dL and 318 μg/dL, but statistically not significant (p >0.05).

AITD, detected with ultrasonography as hypoechogenic thyroid gland, was diagnosed in twenty two (37.3%) patients with PCOS, and in two (10.7%) of the control group (p=0.01). In the PCOS group, eighteen patients were positive for anti-Tg Ab and thirteen for anti-TPO Ab and nine for both. Subclinical hypothyroidism was demonstrated in seven (29.1%) AITD patients, of whom five were in PCOS and two were in the control group. The thyroid function tests of the other patients were normal.

In all study groups, anti-TPO and anti-Tg antibodies were found to be negatively correlated and statistically significant with fasting glucose (r:-0.321, p=0.009; r: -0.263, p=0.02, respectively). Anti-Tg Ab was positively correlated with LH (r: 0.274, p=0.03), and anti-TPO Ab was negatively correlated with DHEAS (r: -0.356, p=0.004) (Figure 1).

Since anti-TPO Ab is more specific for AITD, the data were then analyzed focusing on women with elevated baseline anti-TPO Ab levels in the PCOS group. We found that patients with positive anti-TPO Ab were older and their DHEAS levels were lower than the negative group (p<0.05 and p<0.01, respectively) (Table 3). Although TSH concentration was higher in anti-TPO Ab positive group, it wasn't statistically significant (p=0.06). Negative correlation between anti-TPO Ab and DHEAS was also significant in PCOS patients (r:-0.405, p=0.004).

DISCUSSION

Our study demonstrated that DHEAS levels were lower in PCOS anti-TPO Ab positive patients than negatives. We found that AITD is more prevalent in PCOS patients in accordance with literature. While anti-TG Ab levels were found to be positively correlated with LH, anti-TPO Ab were negatively correlated with DHEAS levels in all

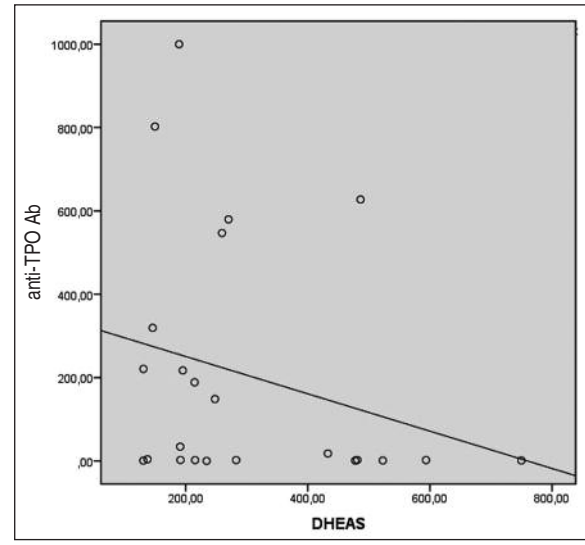

FIGURE 1: Correlation graphic of anti-TPO Ab and DHEAS levels in all study group.
anti-TPO Ab: Anti-thyroid peroxidase antibody.
DHEAS: Dehidroepiandrosteron sülfat.

TABLE 3: Clinical features, laboratory and hormonal results in both TPOAb negative and positive PCOS patients.

	Anti-TPO Ab (-) patients n=38	Anti-TPO Ab (+) patients n=16	p
Age (year)	24.5 (16-33)	27 (20-36)	0.03
F-G score	11 (0-36)	7 (0-20)	NS
Waist (cm)	91.5 (74-119)	94 (72-128)	NS
BMI (kg/m2)	27.1 (19.9-43.7)	28.9 (20.7-40.3)	NS
Glucose (mg/dL)	87 (75-104)	87 (79-109)	NS
HOMA-IR	2.7 (0.8-19.5)	2.8 (0.9-11.7)	NS
Total-C (mg/dL)	186.8 (132.6-280)	214.8 (127-262)	NS
HDL-C (mg/dL)	48 (31-73)	49 (38-80)	NS
LDL-C (mg/dL)	116 (62-196)	125 (66-183)	NS
Tg (mg/dL)	103 (41-408)	114 (41-235)	NS
fT4 (ng/dL)	1 (0.8-1.3)	1 (0.9-1.2)	NS
TSH (µIU/L)	2 (0.3-4.8)	3.3 (0.5-8.8)	NS
LH (µU/mL)	4.9 (0.7-17.9)	7 (4.7-16.2)	NS
FSH (µU/mL)	3.9 (2.6-8.3)	4.7 (1.9-6.4)	NS
Estradiol (pg/mL)	38 (21-132)	53 (33-95)	0.02
Ttest (ng/mL)	0.7 (1.2-1.5)	0.6 (0.3-1.3)	NS
DHEAS (µg/dL)	349.4 (130.2-880)	204.7 (130.4-486.3)	0.009
Androstenedion (ng/mL)	2.9 (0.9-11.9)	3.2 (2-8.1)	NS

F-G: Ferriman-Gallwey; BMI: Body mass index; HOMA-IR: Homeostasis model assessment of insulin resistance; Total-C: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; Tg: Triglyceride; fT4: free thyroxine; TSH: thyroid stimulating hormone; LH: Luteinizing hormone; FSH: Follicule stimulating hormone; Ttest: Total testosterone; DHEAS: Dehydroepiandrosterone sulfate.

participants. To our knowledge, this is the first study that revealed correlation between the anti-TPO Ab and DHEAS in PCOS patients with AITD.

In previous studies, the relationship between PCOS and autoimmunity has been shown by demonstrating increased serologic markers of autoimmunity in patients with PCOS.[5,9,11,21] In our study, we also found higher prevalence of AITD and subclinical hypothyroidism in PCOS patients (37.3%) versus controls (10.7%) in agreement with the previous reports.[9,11,21-23]

LH is a glycoprotein hormone and has a similar alpha subunit with TSH. Human chorionic gonadotropin (hCG) secreted by placenta had been demonstrated to have thyrotrophic effects such as increased TSH receptor expression, thyroid hormone secretion, iodide uptake and organification, adenylate cyclase and deoxyribonucleic acid synthesis in both rats and humans.[24,25] LH had been found to be more potent than hCG on thyrocytes in one of the animal study.[26] In our present study, LH positively correlated with anti-Tg Ab, regardless of age, BMI and HOMA-IR. However, the lack of association of LH with other parameters might be due to small sample size of the participants and the BMI-matched control group.

It had been demonstrated that hypothyroid patients with elevated thyroid autoantibodies and other autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis, serum DHEAS levels were decreased.[16] Additionally, in a recent study DHEA treatment of patients with premature ovarian failure (POF) has been found to decrease anti-TPO Ab levels significantly.[19] Anti-TPO Ab positivity is specific for AITD and believed to reflect intrathyroidal inflammation.[27] DHEA receptors have been shown in T lymphocytes, so it has been speculated that DHEA exerts its effect on immunity directly.[17] Also, DHEA has an indirect effect on immunity by reducing immune cell apoptosis and balancing cytokine levels.[28,29] In AITD, both T-helper cells and thyroid cells are associated with secretion of cytokines.[30] Since tumor necrosis factor (TNF)-±, IL-1 and IL-6 cause activation of the hypothalamic-pituitary-adrenal axis, DHEA may play an important role in the regulation of inflammation. Reciprocally, DHEA can also reduce secretion of cytokine.[31]

In a previous study, it was suggested that elevated anti-TPO Ab levels were associated with poor treatment response in infertile women with PCOS.[12] DHEA supplementation improved ovarian reserve in Hashimoto's thyroiditis,[32] and decreased anti-TPO Ab level in POF patients.[19] Our study clearly shows that increased anti-TPO Ab levels in PCOS patients are associated with low DHEAS concentration. We have known that elevated serum levels of DHEAS has been occur in up to 50% of patients with PCOS,[33,34] and after the age of 30 years, DHEAS declined similarly in both healthy and PCOS women.[35] In our study, low DHEAS levels can be explained with autoimmunity and older age of PCOS group. But we didn't find any correlation between age and DHEAS concentration.

CONCLUSION

As we hypothesized, we found DHEAS levels lower in AITD patients with PCOS. Since these patients were more prevalent in our PCOS group similar to the previous studies, we also demonstrated low DHEAS levels in PCOS patients with higher anti-TPO Ab for the first time. From our results and previous reports, we can conclude that in PCOS patients with low DHEAS levels, we should check thyroid antibodies even if their thyroid function tests are normal. Further follow-up studies with larger number of patients are needed to prove our observation and conclusion.

REFERENCES

1. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007; 370(9588):685-97.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19(1): 41-7.
3. Orio F Jr, Palomba S, Spinelli L, Cascella T, Tauchmanovà L, Zullo F, et al. The cardiovascular risk of young women with polycystic ovary syndrome: an observational, analytical, prospective case-control study. J Clin Endocrinol Metab 2004;89(8):3696-701.
4. Kelly CJ, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JM. Altered vascular function in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002;87(2):742-6.
5. Hefler-Frischmuth K, Walch K, Huebl W, Baumuehlner K, Tempfer C, Hefler L. Serologic markers of autoimmunity in women with polycystic ovary syndrome. Fertil Steril 2010;93(7): 2291-4.
6. Gleicher N, Barad D, Weghofer A. Functional autoantibodies, a new paradigm in autoimmunity? Autoimmun Rev 2007;7(1):42-5.
7. Lee SH, Kim MR, Kim JH, Kwon HS, Yoon KH, Son HY, et al. A patient with combined polycystic ovary syndrome and autoimmune polyglandular syndrome type 2. Gynecol Endocrinol 2007;23(5):252-6.
8. Reimand K, Talja I, Metsküla K, Kadastik U, Matt K, Uibo R. Autoantibody studies of female patients with reproductive failure. J Reprod Immunol 2001;51(2):167-76.
9. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gärtner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol 2004; 150(3):363-9.
10. Du D, Li X. The relationship between thyroiditis and polycystic ovary syndrome: a meta-analysis. Int J Clin Exp Med 2013;6(10):880-9.
11. Garelli S, Masiero S, Plebani M, Chen S, Furmaniak J, Armanini D, et al. High prevalence of chronic thyroiditis in patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2013;169(2):248-51.
12. Ott J, Aust S, Kurz C, Nouri K, Wirth S, Huber JC, et al. Elevated antithyroid peroxidase antibodies indicating Hashimoto's thyroiditis are associated with the treatment response in infertile women with polycystic ovary syndrome. Fertil Steril 2010;94(7):2895-7.
13. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160(4):526-34.
14. Raber W, Nowotny P, Vytiska-Binstorfer E, Vierhapper H. Thyroxine treatment modified in infertile women according to thyroxine-releasing hormone testing: 5 year follow-up of 283 women referred after exclusion of absolute causes of infertility. Hum Reprod 2003;18(4):707-14.
15. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al; Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006;91(11):4237-45.
16. Drbalová K, Matucha P, Matejková-Behanová M, Bílek R, Kríz L, Kazihnitková H, et al: Immunoprotective steroids and SHBG in non-treated hypothyroidism and their relationship to autoimmune thyroid disorders. Physiol Res 2008;57 Suppl 1:S119-25.
17. Crosbie D, Black C, McIntyre L, Royle PL, Thomas S. Dehydroepiandrosterone for systemic lupus erythematosus. Cochrane Database Syst Rev 2007;17(4):CD005114.
18. Hazeldine J, Arlt W, Lord JM. Dehydroepiandrosterone as a regulator of immune cell function. J Steroid Biochem Mol Biol 2010; 120(2-3):127-36.
19. Ott J, Pecnik P, Promberger R, Pils S, Seemann R, Hermann M, et al. Dehydroepiandrosterone in women with premature ovarian failure and Hashimoto's thyroiditis. Climacteric 2014;17(1):92-6.
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412-9.
21. Sinha U, Sinharay K, Saha S, Longkumer TA, Baul SN, Pal SK. Thyroid disorders in polycystic ovarian syndrome subjects: a tertiary hospital based cross-sectional study from Eastern India. Indian J Endocrinol Metab 2013;17(2):304-9.
22. Benetti-Pinto CL, Berini Piccolo VR, Garmes HM, Teatin Juliato CR. Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal, and metabolic parameters. Fertil Steril 2013; 99(2):588-92.
23. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87(2):489-99.
24. Hershman JM. Role of human chorionic gonadotropin as a thyroid stimulator. J Clin Endocrinol Metab 1992;74(2):258-9.
25. Kraiem Z, Sadeh O, Blithe DL, Nisula BC. Human chorionic gonadotropin stimulates thyroid hormone secretion, iodide uptake, organification, and adenosine 3',5'-monophosphate formation in cultured human thyrocytes. J Clin Endocrinol Metab 1994;79(2):595-9.
26. Yoshimura M, Hershman JM, Pang XP, Berg L, Pekary AE. Activation of the thyrotropin (TSH) receptor by human chorionic gonadotropin and luteinizing hormone in Chinese hamster ovary cells expressing functional human TSH receptors. J Clin Endocrinol Metab 1993;77(4):1009-13.
27. Weetman AP, McGregor AM. Autoimmune thyroid disease: further developments in our understanding. Endocr Rev 1994;15(6):788-830.
28. Liu C, Zhou H, Qu R, Liu Z. Effects of sex hormones on apoptosis in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. Chin Med J (Engl) 2001;114(3):291-3.
29. Chang DM, Chu SJ, Chen HC, Kuo SY, Lai JH. Dehydroepiandrosterone suppresses interleukin 10 synthesis in women with systemic lupus erythematosus. Ann Rheum Dis 2004; 63(12):1623-6.
30. Weetman AP. Cellular immune responses in autoimmune thyroid disease. Clin Endocrinol (Oxf) 2004;61(4):405-13.
31. Schwartz KE. Autoimmunity, dehydroepiandrosterone (DHEA), and stress. J Adolesc Health 2002;30(4 Suppl):37-43.
32. Benvenga S, Trimarchi F. Changed presentation of Hashimoto's thyroiditis in North-Eastern Sicily and Calabria (Southern Italy) based on a 31-year experience. Thyroid 2008;18(4): 429-41.
33. Hoffman DI, Klove K, Lobo RA. The prevalence and significance of elevated dehydroepiandrosterone sulfate levels in anovulatory women. Fertil Steril 1984;42(1):76-81.
34. Carmina E, Rosato F, Jannì A. Increased DHEAs levels in PCO syndrome: evidence for the existence of two subgroups of patients. J Endocrinol Invest 1986;9(1):5-9.
35. Pall M, Azziz R, Beires J, Pignatelli D. The phenotype of hirsute women: a comparison of polycystic ovary syndrome and 21-hydroxylase-deficient nonclassic adrenal hyperplasia. Fertil Steril 2010;94(2):684-9.