Relation between thyroid disorders and polycystic ovary syndrome

***Abdulrazak H. Alnakash ** Suhayla Abass ***Sahar Jassim Abid**
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Abstract:

Background :

Polycystic ovarian syndrome which is the most common endocrinopathy of women at their reproductive age seems to be associated with thyroid dysfunction, but it's true pathogenesis is far from being elucidated. Both have independent risks of ovarian dysfunction and pregnancy related complications.

Objective: To evaluated the association between thyroid dysfunction and polycystic ovary syndrome (PCOS).

Study Design: Prospective Case-Control Study.

Setting : Department of Obstetrics and Gynecology/ AL-Elwiya Maternity Teaching Hospital, Baghdad - Iraq

Patients and Methods: The study included 100 women at reproductive age, 50 of them were defined as having polycystic ovary syndrome (study group), another 50 healthy women served as control group. Thyroid function and morphology were evaluated by measuring serum thyroid stimulating hormone (TSH), free thyroxine levels (free T3 and free T4), anti-thyroperoxidase antibody (anti-TPO Antibody) and *anti-thyroglubulin antibody (anti-TG Antibody)* and by clinical and ultrasound examination of thyroid gland.

Results: The study revealed statistically higher prevalence of autoimmune thyroiditis in patients with PCOS (12% vs. 4% of control) as evidenced by raised anti-TPO antibody levels (means125.91±333.39 and 88.19±316.18 respectively; *P* =0.563). PCOS patients were found to have higher mean TSH level than that of the control group (3.14±2.74and 2.24±1.81respectively; *P* value < 0.05). There was high prevalence of goiter among PCOS patients (10.0%vs. 4% of control, *P* value > 0.001). On thyroid ultrasound, a significantly higher percentage of PCOS patients (10%; controls 2.5%) had hypoechoic ultrasound pattern which also compatible with diagnosis of autoimmune thyroiditis.

Conclusions: Higher prevalence of thyroid disorders in the form of autoimmune thyroiditis in patients suffering from PCOS (12%) compared with control group (4%).

Key words: Polycystic ovarian disease; Thyroid, Autoimmune; Antibody

Introduction:

Polycystic ovarian syndrome (PCOS) represents heterogeneous collection of signs and symptoms forms a spectrum of disorders with mild presentation in some but severe disturbance of reproductive, endocrine and metabolic function in other. Diagnosis of PCOS is made according to Rotterdam consensus when two out of three following criteria are present:- Oligomenorrhea and/ or anovulation, clinical or/and biochemical sign of hyperandrogenism and Polycystic ovaries assessed by ultrasound, with 12 or more follicles measuring 2-9 mm in diameter and increased ovarian volume (>10 cm^3) (1,2).

Insulin resistance & hyperinsulinaemia are characteristic of both obese and non-obese PCOS patients which augments androgen production. Via LH stimulation of ovarian receptors of insulin and insulin - like growth factors leads to increased androgen production in thecal cells (3,4). Insulin also acts by enhancing the amplitude of serum LH pulses (5), Prolactin levels are elevated in about 25% of patients with PCOS (6).

Thyroid hormones are present in follicular fluid and in granulosa cells (7). In cases of hyperthyroidism, the ultrasonography appearance of the ovaries shows an abnormal size, form, and number of follicle. The appearance become normal after treatment. Multicystic ovaries during profound hypothyroidism has also been noticed which suggest a direct effect of thyroid hormones on the ovary. Thyroid stimulating hormone receptor in the ovary is up-regulated by gonadotropin-driven cascade and down-regulated by estradiol. Recently discovered glycoprotein thyrostimulin is expressed in the ovary and was shown to activate ovarian Thyroid stimulating hormone receptor expression, suggesting a paracrine regulation of thyroid function in the ovary (8). Hypothyroidism influences ovarian function by decreasing levels of sex-hormone-binding globulin and increasing the secretion of prolactin. In women of reproductive age, hypothyroidism can be reversed by thyroxine therapy to improve fertility and avoid the need for use of assisted reproduction technologies (9). Infertility and reproductive impairment can be related to abnormalities in the endocrine or immune system, or both. These systems are also directly linked to the thyroid gland since thyroid autoimmunity (TAI) is the most frequent cause of hypothyroidism in women of reproductive age (10). Early stages of thyroid dysfunction before symptoms can lead to subtle change in ovulation and endometrial receptivity, which may have profound effect on fertility. Primary ovarian failure can also be seen in patients with Hashimoto's thyroiditis as a part of autoimmune polyglandular syndrome. Rarely, in primary hypothyroidism, secondary depression of pituitary function may lead to ovarian atrophy and amenorrhoea (11). Aim of Study is to study the relationship between thyroid disorders and polycystic ovary syndrome

Patients and Methods:

This study included 100 women aged 14-40 years (50 women with PCOS and 50 healthy women served as control) were selected while attending the Gynecology clinic in AL-Elwiya Maternity Teaching Hospital during the period from 1st Mar. to end of Nov. 2014 The study was

approved by the Iraqi Board for Medical Specialization and hospital administration.

verbal consent was obtain from the participants after explaining to them the purpose and procedures of the study.A questionnaire sheet was designed to included detailed history about menstrual history menstrual disturbances were classified as oligomenorrhea (8 cycles/year or more, menstrual interval 35 days) and amenorrhea (absences of menses in the last 6months or more).Gynecological, infertility history, medical history, social & family history, hair growth, weight, acne, endocrine abnormality and history of thyroid dysfunction or surgery and any medication taken for thyroid disorder.Also clinical examination was done included vital signs (Blood pressure, pulse rate, temperature, respiratory rate).thyroid ultrasound for patients with goiter . thyroid gland assessment looking for signs of hyper or hypothyroidism followed by pelvic and All the women were weighted by electrical scale and body mass index calculated according to equation

$$\text{BMI} = \frac{\text{Mass(kg)}}{\text{Height(m)}^2}$$

BMI of 18.5 to 25 indicates optimal body weight while lower than 18.5 is underweight and above 25 is overweight and above 30 is obesity.

The Rotterdam classification was used to define the study group. Evidence of hyperandrogenism: acne, seborrhea, alopecia and hirsutism (Modified Ferryman-Galway was used to assess the degree of hirsutism).

A score of at least 6 was taken as significant. Biochemical hyperandrogenemia was defined by elevated Serum testosterone and menstrual behavior (oligomenorrhea or amenorrhea) and ultrasound feature of PCO were considered when including participants.

Laboratory investigations like serum LH, FSH, thyroid stimulating hormone (TSH), free thyroxine levels (free T3 and free T4),), measured by ELISA were performed in both PCOS and control population in our hospital laboratory.Normal serum levels of different hormones and peptide were defined as free T3=0.92-2.33 nml/L,freeT4=60-120 nml/L,TSH (Euthyroid= 0.25-5 ulU/ml, hypothyroidism:>7.0 ulU/ml and hyperthyroidism:<0.15 ulU/ml prolactin-1.9-25 ng/ml,Testosterone=0.1-0.9 ng/ml, LH = 2.0- 8mlU/ml, FSH = 3.9-24.0 mlU/ml, LH and FSH were measured on the 2nd day of menstruation .

Another samples were collected for anti-thyroperoxidase antibody (anti-TPO Antibody), anti-thyroglubulin antibody (anti-TG Antibody) these samples were left to stand at room temperature for at least 30 minutes to allow the blood to clot and then centrifuged for 10 minutes then freezing at – 20 C0 and kept there without thawing till the day of testing then serum measured using ELISA sandwich kits

had be done in outer laboratory with the range of the assay for anti –TPO was < 80 IU/MLas normal value, 80-200 equivocal, and > 200 considered positive and for anti-TG Antibody was < 50 IU/ML as normal ,50-75 equivocal ,and > 75 +ve .

Thyroid ultrasound was performed using a 7.5 MHz transducer with duplex sonography ,thyroid disorders were diagnosed with assented of the physician in our hospital Dr Anmar Deyaaldin

The control group consisted of 50 healthy women with regular cycle and no clinical and ultrasonographic features of PCOS.

All collected data of questionnaire were gathered ,analyzed and arranged for subsequent study.

Exclusion Criteria :

-pregnant woman .

- Women with known condition of secondary /tertiary hypothyroidism

-Women with known condition of congenital adrenal hyperplasia or adrenal disease.

Statistical Analysis:

Statistical package for social sciences version 20 (SPSS 20) was used for data input and analysis. Continuous variables presented as means and discrete variables presented as numbers and percentages. T test for two independent samples were used to test the significant of difference in means. Chi-square test for independence and Fisher's exact tests were used to test the significance of association between discrete variables. Binary logistic regression analysis was used to measure Odds Ratios (OR). Findings with P values less than 0.05 were considered significant.

Results :

Sample Description: The study sample composed of 50 patients with PCOS and 50 control females (not having PCOS). Age of all participants varied from 14 to 40 years old. In this study population maximum numbers of PCOS patients were in the age group of 15-20 years (32 patients; 40%) followed by 26-30 years (24 patients; 30%).

Table 1, Shows Clinical Characteristics of PCOS patients and control group, 27 (54.0%) of PCOS patients and 29

(58.0%) of control are married. Out of married participants; around 59% of PCOS and 21% of control have a history of abortion with no significant association between PCOS status and history of abortion (P > 0.05,).A significant finding that PCOS patients had oligomenorrhea and all of control had regular cycle (P < 0.05).Regarding hirsutism score; mean score was significantly higher in PCOS group (13.6±5.1) than control (5.0±2.19) (P < 0.05). This score indicated that 84% of PCOS had moderate to severe hirsutism status while only two (4%) from the control group had moderate to severe hirsutism, and this observation was significant (P < 0.05).ass index (BMI) significantly had higher mean (29.8 kg/m^2) in PCOS group than in control group (26.2 kg/m^2) (P < 0.05). The frequency of obesity was significantly observed more in PCOS (40%) group compared to 10% in control group and overweight was more observed in control females (60%) compared to 54% in PCOS group (P < 0.05).

Table 1: Clinical Characteristics of study sample:

	Study Group				P value
	PCOS		Control		
Variables	N=50	100.0%	N=50	100.0%	
History of abortion among married					0.176
Positive	10	58.8%	6	20.7%	
Negative	17	41.2%	23	79.3%	
Menstrual Cycle					< 0.001
Oligomenorrhea	50	100.0%	0	0.0%	
Regular Cycle	0	0.0%	50	100.0%	
Hirsutism Score; mean±SD	13.6±5.1		5.0±2.19		< 0.001
Interpretation of hirsutism score					< 0.001
Normal	5	10.0%	39	78.0%	
Mild	3	6.0%	9	18.0%	
Moderate	21	42.0%	1	2.0%	
Severe	21	42.0%	1	2.0%	
BMI (Kg/m^2) ; mean±SD	29.8±4.1		26.2±2.4		< 0.001
BMI Category					0.330
Under weight	0	0.0%	0	0.0%	
Normal	3	6.0%	6	12.0%	
Overweight	27	54.0%	30	60.0%	
Obese	20	40.0%	14	28.0%	
Goitre	5	10.0%	2	4.0%	0.239

Table 2, Describes findings related to gonadotrophines, prolactine and androgen: FSH:Mean levels did not vary between study groups (P > 0.05), there was no significant association between FSH status between the groups (P > 0.05). LH:Mean level was significantly higher in PCOS group than in control (11.76& 3.19 mIU/ml in PCOS and control respectively) (P < 0.05). increased levels of LH are more frequent in PCOS group (62%) than in control (4%) (P < 0.05, table 3). Prolactin: PCOS did not exhibit any significant influence upon mean prolactin level (14.17 & 10.73 ng/ml in PCOS and control respectively) (P > 0.05).Vast majority of PCOS group (98%) and all of control group (100%) had normal prolactin levels. Testosterone showed no significant difference in its mean level between the two study groups (1.21 & 1.17 ng/ml in PCOS and control respectively) (P > 0.05). Though the proportion of increased testosterone level in PCOS group (72%) is higher than in control (60%); this finding was not significant (P> 0.05).

Table 2: gonadotrophines, prolactine and androgen levels in both groups :

Variables	Study Group				P value
	PCOS		Control		
	N=50	100.0%	N=50	100.0%	
FSH (mIU/ml); mean±SD	5.45±2.45		4.87±2.43		0.237
FSH Status					0.271
Normal	38	76.0%	33	66.0%	
Increased	12	24.0%	17	34.0%	
Decreased	0	0.0%	0	0.0%	
LH (mIU/ml) ; mean±SD	5.76±4.84		3.19±3.04		0.002
LH Status					0.009
Normal	11	22.0%	31	62.0%	
Increased	31	62.0%	2	4.0%	
Decreased	8	16.0%	17	34.0%	
Prolactin (ng/ml) ; mean±SD	14.17±5.89		10.73±7.35		0.246
Prolactin Status					1.000*
Normal	35	70.0%	50	100.0%	
Increased	14	28.0%	0	0.0%	
Decreased	1	2.0%	0	0.0%	
Testosterone (ng/ml) ; mean±SD	1.21±0.37		1.17±0.81		0.751
Testosterone Status					0.205
Normal	14	28.0%	20	40.0%	
Increased	36	72.0%	30	60.0%	
*after merging categories into normal and other than normal.					

Table 3, indicators of thyroid function (T3, T4, TSH, TG & TPO) of PCOS patients and control group showed no significant variation in mean level between study groups nor significant associations with PCOS status (P > 0.05), raised anti-TPO and anti-TG antibody levels (means125.91±333.39 and88.19±316.18 respectively; P =0.563). PCOS patients higher mean TSH level than control group (3.14±2.74and 2.24±1.81respectively; P < 0.05). There was high prevalence of goiter (multinodular goiter) among PCOS patients (10% vs. 4% of control, P < 0.001

Table 3: Laboratory findings related to the thyroid function:

Variables	Study Group				P value
	PCOS		Control		
	N=50	100.0%	N=50	100.0%	
T3 (nml/L) ; mean±SD	1.60±0.46		1.61±0.35		0.949
T3 Status					0.307*
Normal	47	94.0%	49	98.0%	
Decreased	1	2.0%	0	0.0%	
Increased	2	4.0%	1	2.0%	
T4 (nml/L) ; mean±SD	78.60±12.64		76.98±20.03		0.631
T4 Status	49	98.0%	47	94.0%	0.307*
Decreased	1	2.0%	3	6.0%	
Increased	0	0.0%	0	0.0%	
TSH (uIU/ml) ; mean±SD	3.14±2.74		2.24±1.81		0.055
TSH Status					0.182*
Normal	43	86.0%	47	94.0%	
Decreased	0	0.0%	1	2.0%	
Increased	7	14.0%	2	4.0%	
TG (IU/ml) ; mean±SD	207.77±600.30		76.18±191.56		0.143
TG Status					0.218*
Normal	42	84.0%	46	92.0%	
Equivocal	0	0.0%	1	2.0%	
Positive	8	16.0%	3	6.0%	
TPO (IU/ml) ; mean±SD	125.91±333.39		88.19±316.18		0.563
TPO Status					0.276
Normal	39	78.0%	44	88.0%	
Equivocal	3	6.0%	3	6.0%	
Positive	8	16.0%	3	6.0%	

Figure 1, shows the Mean levels of Thyroid function indicators ,anti-TPO and anti-TG according to study groups in PCOS patients and non-PCOS patients.

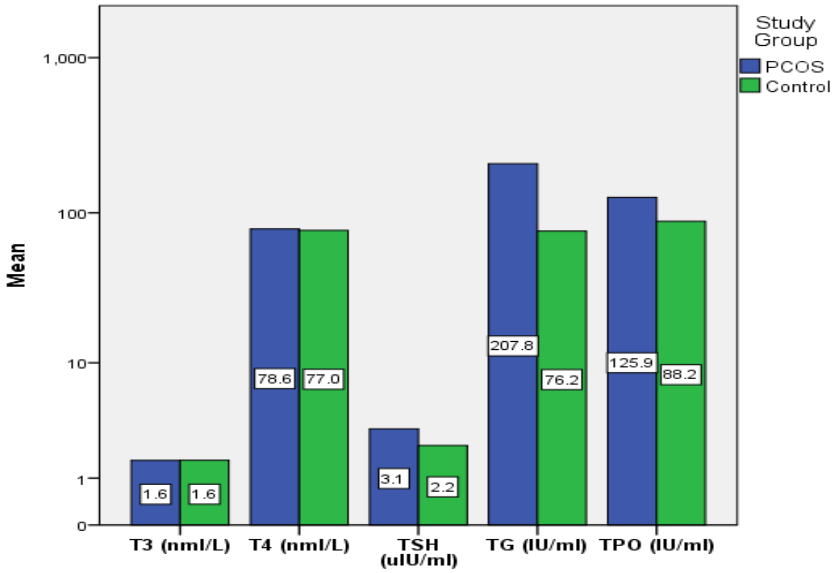

Figure 1: Mean levels for Thyroid function indicators according to study group.

Figure 2, shows the results of thyroid function hormones and antithyroid antibodies (anti-TPO and anti-TG) according to study group, and status of each hormone of thyroid function ,there is no deference in T3and T4 level in PCOS patients and control group but there is slight increase in TSH level in PCOS patients about 14% vs 4% in control group and there is slight increase in antithyroid antibodies (anti-TPO and anti-TG) about 16% vs 6% in control group .

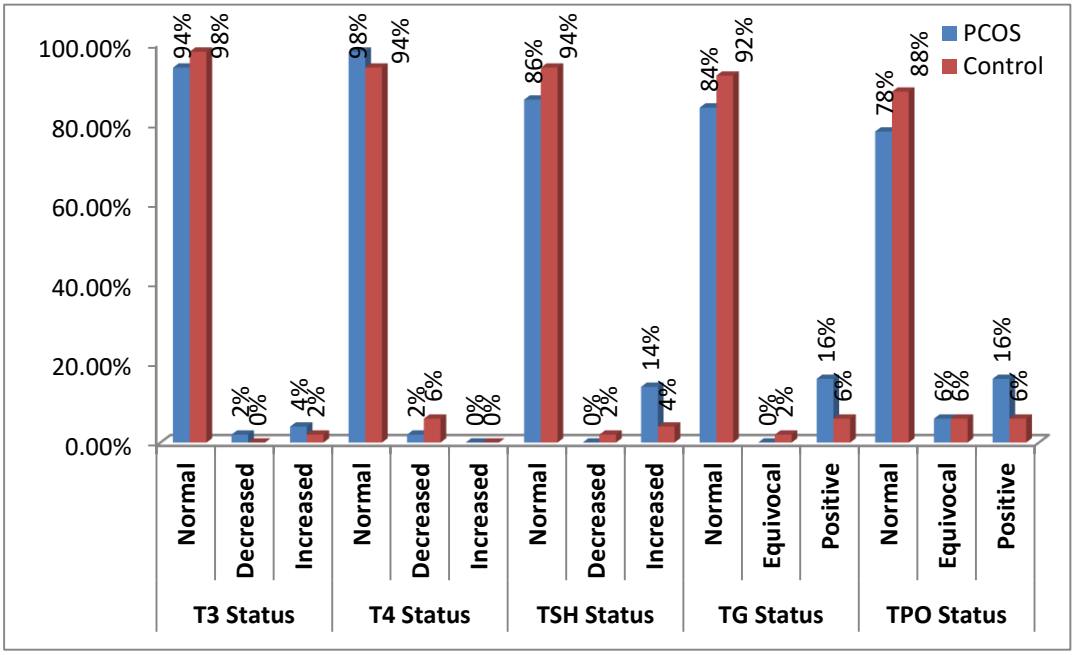

Figure 2: status of thyroid function of the studied groups.

Results of logistic regression analysis:

Biochemically thyroid disorders were detected in 8 (16 %) out of 50 patients with PCOS as compared to only 3 of control population (6 %) P < 0.05. Subclinical hypothyroidism was detected in 6 patients (12 % vs 6% of control), 2 patients had clinically overt hypothyroidism (4 %), and autoimmune thyroiditis was detected in 6 patients (12% vs. 6% of control) as evidenced by raised anti-TPO antibody levels (means125.91±333.39 and88.19±316.18 respectively; P =0.563). PCOS patients higher mean TSH level than control group (3.14±2.74and 2.24±1.81respectively; P < 0.05). There was high prevalence of goiter (multinodular goiter) among PCOS patients (10% vs. 4% of control, P < 0.001). none of PCOS patients nor control had features of Graves' disease. On thyroid ultrasonograph, a higher percentage of PCOS patients (10 %; controls 4 %) had hypoechoic scan pattern compatible with the diagnosis of autoimmune thyroiditis.

Despite that the measure OR expressed the likelihood of more than twice to have increased TSH, positive TG and positive TP on being a PCOS patient; such findings were not found significant according to this study (P > 0.05).

Table 4: Logistic regression analysis for the relationship PCOS on thyroid function:

Dependent Variables	P value	OR	95% CI for OR	
			Lower	Upper
Increased TSH	0.118	3.500	0.727	16.848
Positive TG	0.147	2.667	0.707	10.052
Positive TPO	0.147	2.667	0.707	10.052
Background levels: non increased for TSH, other than positive for positive TG, and other than positive for positive TPO.				

Discussion:

In this study, the age of patients with PCOS ranged between 15-23 years and has decreased significantly after age of 30. This may be due to the fact that, menstrual symptoms begin from puberty itself which leads to early presentation in the PCOS. According to modified Ferriman–Gallwey score, clinical hirsutism was present in 84.5% of the patient.

Raised serum free testosterone was detected in 72% patients. This finding correlates with other studies done by Yeon-Ah Sung *et al* who showed that 60.7% of PCOS had hyperandrogenemia, 75.1% had hirsutism (12). Menstrual disturbance in form of oligomenorrhoea or amenorrhoea was seen in all study group (100%), but Carmina E ,*et al*. reported 60-85% of the patients suffering from gross menstrual dysfunction (13).

LH level was elevated in 62.4% of participants similar figures seen in study done by Banaszewaska, *et al* (50) . Uma Sinha, *et al*. found that 44 patients from 88 (55%) had elevated LH to FSH ratio above 2.0 (14).

Prolactine hormone level in this study show no significant difference in its mean level between the two study group (14.17 & 10.73 ng/ml in PCOS and control respectively) (P> 0.05), this goes with the study done by Johanna Schmidt, *et al*. who found that prolactin level similar in PCOS women and controls (15)

Body mass index (BMI) significantly had higher mean (29.8 kg/m^2) in PCOS group than in control group (26.2 kg/m^2) (P < 0.05). The frequency of obesity was significantly observed more in study group (40%) compared to (10%) in control group and overweight was more observed in control females (60%) compared to (54%) in PCOS group (P < 0.05) and These findings are close to the study done by Uma Sinha, *et al.* in which 44 patients (55%) had BMI of more than 25 *(14).*

The thyroid hormones (T3, T4) appear normal in 94-98% in both group showed no significant variation in mean level between study groups nor significant associations with PCOS status (P > 0.05) but TSH level raised in 14% of study group and 4% of control , PCOS patients have higher mean TSH level than control group (3.14±2.74 and 2.24±1.81respectively; P < 0.05) this goes with the results of Raghad Al-Saab , *et al* who recorded that TSH, T3 and T4 of the patients with PCOS and the controls did not differ significantly(16). But does not agree with Melia Karaköse , *et al* who stressed that TSH level in pcos patients and control groups did not differ significantly (1.9±1.2 µIU/mL vs. 1.8±0.9 µIU/mL,p=0.475) and the serum levels of T3 and T4 in the control group were significantly lower than in the patient group (T3: 2.7±0.3 pg/mL vs. 2.9±0.3 pg/mL, p=0.02 T4: 1.0±0.1 ng/dL vs. 1.1±0.1 ng/dL, p=0.03) (17).Anti-TPO and anti-TG antibody levels (means125.91±333.39 and 88.19±316.18 IU/mL respectively; P =0.563) show clear difference, although not significant between

study and control group about 16% vs 6% in control group. In study done by Melia Karaköse , *et al* who reported that Mean ±SD serum anti-TPO Antibody in the PCOS patients and controls was 134±254 IU IU/mL and 169±300 IU/mL, respectively and the mean±SD of serum anti- TG Antibody in PCOS patients and controls was 56±83 and 70±77 IU/mL, respectively, there was no significant difference between patients and the control group in terms of anti-TPO Antibody levels and anti-TG Antibody levels (p=0.49 and p=0.324, respectively) , the control group had a higher prevalence of anti-TG Antibody than PCOS (24 vs. 15%); the divergence was not statistically significant (p=0.17) , the prevalence of subjects with positive anti-TPO Antibody in the patient and control groups was 44 and 73%, respectively; it was significantly higher in control group (p=0.01)(17).

In study done by Ozdemir D *et al.* the mean ± SD of serum anti-TPO Antibody in PCOS patients and subjects in the control group was 216 ± 428 and 131 ± 364 IU/ml respectively (*P* = 0.04) but serum levels of TSH and anti-TG (thyroglobulin) antibody in both the groups were not much different (18) .

Thyroid disorders, involved Subclinical hypothyroidism was present in 12% of study gruop while clinical hypothyroidism was present in 4% of cases. All of those Subclinical hypothyroid patients were autoimmune hypothyroidism with goiter (multinodular goiter) which was present in 10% of study group compared 4% of control. Thus revealed higher prevalence of thyroid disorders among study gruop compared to age matched controls. The findings obtained from this work go with the study performed by Uma Sinha, *et al*., where they observed that subclinical hypothyroidism was present in 22.5% and clinical hypothyroidism was present in 2.5% cases, among these hypothyroid patients, autoimmune hypothyroidism was present in 22.5% patient, and goiter was present in 27.5% patient and other study by Janssen, *et al*. where they observed a prevalence of autoimmune thyroiditis in 26.9% of their 175 patients (19). Other studies reported higher prevalence of autoimmune thyroiditis in PCOS subjects, Didem Ozdemir, *et al*. among 107 patients found a prevalence of 30.5% and thyroid nodules were detected in 29 (27.1%) patients, 10 had solitary and 19 had multiple nodules, thyroid pathologies were observed in half of the patients with PCOS (18). Among the most recently held studies done by Kachuei, *et al*. from Iran has also shown significantly higher prevalence of autoimmune thyroiditis and goiter in PCOS patients than that in control subjects (62.3% vs. 35.7%, *P* = 0.0001)(20).

Unuane D *et al*. reported that the mean ± SD of serum anti-TPO Antibody in PCOS patients and subjects in the control group was 216 ± 428 and 131 ± 364 IU/mL respectively (*P* = 0.04) but serum levels of TSH and anti-TG (thyroglobulin) antibody in both groups were not different (21).

Conclusion:

Although the cause-effect relationship between PCOS and thyroid disease remains unknown, a higher prevalence of thyroid disorders in the form of autoimmune thyroiditis is found in patients suffering from PCOS (12%) compared with control group (4%)

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*Consultant OBGYN
Alkindy Medical College/ Baghdad University
Al-Elwiya Maternity Teaching Hospital
Razaknakash@yahoo.com
+964 7901311564

**Registrar at Al-Elwiya Maternity Teaching hospital
Candidate of the Iraqi Counsel for medical specialization

***Specialist in OBGYN Al-Elwiya Maternity Teaching Hospital
Lecturer At Alkindy Medical College/ Baghdad University
saharjassem@yahoo.com
+9647809031100