RESEARCH ARTICLE

Thyroid hormonal changes among women with polycystic ovarian syndrome in Baghdad – a case-control study [version 1; peer review: 1 approved with reservations, 2 not approved]

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Abstract

Background: Polycystic ovarian syndrome is a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and polycystic ovary morphology. The prevalence of polycystic ovaries on ultrasound is around quarter of all women but is not associated with the full syndrome. The study aimed to assess the status of thyroid disorders in polycystic ovarian syndrome (PCOS).

Methods: This prospective hospital-based case-control study involved most outpatients aged 13–45 years who visited the Obstetrics, Gynecology, and Infertility clinic at Baghdad Teaching Hospital with complaints of hirsutism and/or oligomenorrhea or infertility. This study included 70 patients, including 50 with PCOS (PCOS group) and 20 without (control group).

Results: The PCOS group exhibited significantly higher mean thyroid stimulating hormone level (3.9 vs. 3.1 μ IU/L), luteinizing hormone level (15.2 vs. 4.7 mIU/mL), and body mass index (28.6 vs. 24.9 kg/m²; all, $p < 0.001$) and a non-significantly higher follicle-stimulating hormone level (9.2 vs. 5.2 mIU/L) than the control group.

Conclusion: Our results demonstrate a higher prevalence of thyroid disorder among women with PCOS.

Keywords

Polycystic ovary syndrome, subclinical hypothyroidism, thyroid hormone

Open Peer Review

Approval Status

	1	2	3
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Introduction

Polycystic ovarian syndrome (PCOS) is a condition of ovarian dysfunction characterized by hyperandrogenism and polycystic ovaries. The global prevalence of polycystic ovaries among women is 25%¹. PCOS is a state of insulin resistance, which is considered to be the main factor contributing to development of the syndrome; diagnosis is based on the presence of two out of three of the following: clinical and/or biochemical androgen excess, anovulation and polycystic ovaries on pelvic ultrasound². The mechanisms behind these include hyperinsulinemia, disruption of the hypothalamic–pituitary–gonadal axis, dysregulation of ovarian steroidogenesis, as well as genetic and environmental factors^{2,3}. PCOS mainly affects women in aged 18–35^{3,4}. Previous studies have documented ovarian enlargement and cystic transformation in thyroid disorders^{5–8}. Thyroid disorders and PCOS are of widespread in the general population, however, the precise nature of the relationship between the two disorders is not currently known. Although the pathophysiology of thyroid disorder and PCOS are totally different⁶. Whether this is due to some common factors predisposing an individual to both disorders, or due to a pathophysiological connection between the two disorders has yet to be established⁵. Two factors making the picture more interesting, are that both have different etiopathology, and that reportedly thyroid disorders are more common in PCOS subjects^{7–9}. PCOS begins soon after menarche age as an endocrinologic abnormality, two most common endocrine symptoms are chronic elevation of luteinizing hormone (LH) and insulin resistance^{4,7,9}. The genetic cause of high LH is unknown. Interestingly, neither an elevation in LH nor insulin resistance alone is enough to initiate the PCOS^{7,9}. High LH and hyperinsulinemia work synergistically, causing ovarian growth, androgen production, and ovarian cyst formation^{4,5,9}. The thyroid gland regulates the rate at which the body converts food for energy, functioning as a thermostat to control the body's metabolism and other systems. If it secretes hormones too fast will increase metabolism and lead to hyperthyroidism, the inverse leads to slow metabolism, resulting in weight gain and hypothyroidism^{4,5}. However, it is not yet known whether this is because of factors predisposing an individual to both disorders or a pathophysiological connection between the two disorders.

Methods

Study design and setting

This hospital-based case-control study was conducted at the Obstetrics, Gynecology, and Infertility clinic at Baghdad Teaching Hospital. The study took place from January to October 2018. We obtained a medical and surgical history, a complete menstrual history, including menarche and family history of PCOS, and history of hirsutism, acne, alopecia, menstrual irregularities, or infertility, also history about last pregnancy and abortion. Any history of headaches or blurred vision, any signs or symptoms of thyroid dysfunction include acne, hirsutism, deepening of the voice, and increase in muscle mass were recorded. Thyroid hormone levels were tested to rule out thyroid disease as an etiology of anovulation, and LH and follicle-stimulating hormone (FSH) also analyzed.

Participants and eligibility criteria

The study included 50 subjects diagnosed with PCOS and 20 control subjects, who consented to participate of individuals

attending the hospital for follow up, treatment and further evaluation. In accordance with the Rotterdam criteria¹⁰, PCOS was defined by the presence of any two of the following conditions

Participant inclusion criteria:

1. Irregular menstruation: no menses in the past 6 months or menstrual cycle prolonged for more than 35 days
2. Increased androgen levels and/or acne and/or alopecia (androgenic pattern)¹¹ or biochemical hyperandrogenism (testosterone level >2.0 nmol/L)
3. Polycystic ovaries (follicles 2–9 mm in diameter and ≥12 in number or ovarian volume ≥10 cm³) identified by transabdominal pelvic ultrasonography after excluding other diseases such as congenital adrenal hyperplasia and virilizing tumors¹².

Participant exclusion criteria:

1. Patients use steroids.
2. Patients on contraceptive pills.
3. Pregnancy
4. Very low body mass index by measuring BMI [Normal (18.6–24.9)m²/Kg, and below that is underweight].
5. Hyperthyroidism, or hypothyroidism (TSH ; normal (0.35 to 5 mU/L), T4; normal (6–12 µg/d), T3; normal (260–480 pg/mL) tests).
6. Neoplasia: thyroid or adrenal (cancer diagnosis via lab tests as above and imaging as MRI, CT scan, PET scan and thyroid scan).

Control inclusion criteria:

1. Healthy. Good physical, mental, or emotional state
2. Not using of any form of medication.
3. Good performance status.

Control exclusion criteria:

1. Diabetic.
2. Positive past-medical history (hypertension, cardiovascular diseases, renal diseases, etc.).
3. Positive past-surgical history (any surgical procedures as thyroidectomy, nephrectomy, hysterectomy etc.). The control haven't any diseases or operations in past history.

Data collection

All patients were assessed by complete history-taking and clinical examination include general, inspection, palpation, auscultation, neurologic, and ophthalmologic examination. For thyroid hormone analysis, 5 mL of venous blood was collected from each patient, at the Obstetrics, Gynecology, and Infertility clinic

at Baghdad Teaching Hospital, and when patients attended hospital. This was performed by lab staff by using tourniquets and syringe to collect venous blood. All samples collected from venous blood from arm into tubes. Samples were checked for complete clot formation prior to centrifugation, and for particulate matter prior to analysis. If the assay was performed within 24 hours after collection, the specimen was stored at 2–8°C. If testing was delayed more than 24 hours, the specimen was separated from the clot or red blood cells and stored frozen (–10°C or colder). Specimens were mixed thoroughly after thawing, by gently inverting, and then centrifuged, to ensure consistency in the results. Special care must be taken to prevent contamination. 150 µl of specimen was the minimum volume required to perform the assay. The dilution was performed so that the diluted test results read greater than the sensitivity of the assay, and the concentration of hormones were determined by multiplying the concentration of the diluted sample by the dilution factor (conc. x 10 times dilution). Hormone analysis included estimation of serum free triiodothyronine (T3) [LOT No.: 004206], free tetraiodothyronine (T4) [LOT No.: 003192], thyroid stimulating hormone (TSH) [LOT No.: 001285], luteinizing hormone (LH) [LOT No.: 004211], follicle-stimulating hormone (FSH) [LOT No.: 003701], progesterone, and estradiol [LOT No.: 005481], all these tests measured after collect blood from patients and controls, using (SIEMENS/ ADVIA Centaur®) REF: 03852677 (112219) SMN by Siemens healthcare diagnostics Ltd.

Statistical analysis

Data entry and analysis were performed by using SPSS version 23. Numerical data were expressed as mean±standard deviation and categorical data as percentage. The level of significance, set at $p \leq 0.05$, was confirmed by the Student t-test.

Ethical considerations

The Medical Ethical Committee of Baghdad University / College of Pharmacy approved this study (code:100123). Written informed consent was taken from participants upon presentation to the hospital to both participate in the study and for the research team to access their medical records.

Results

The average age of participants was 27.7 ± 4.7 years for the PCOS group and for the control group 26.8 ± 4.7 years. All patients lived in urban cities in Baghdad province. The PCOS group exhibited significantly higher mean body mass index (BMI; 28.6 vs. 24.9 kg/m²) and LH level (15.2 vs. 4.7 mIU/mL) and a non-significantly higher FSH level (9.2 vs. 5.2 mIU/L) than the control group, (P-values <0.001 , <0.001 , <0.007 , <0.001 , respectively) (Table 1 and Underlying data¹³). There was a significant association between (P-value <0.003) increased body weight and PCOS; while 86% of patients in the PCOS group were overweight or obese, the proportion of overweight/obese patients in the control group did not exceed 50% (Table 2, Table 3). The proportion of patients with elevated TSH levels was significantly greater in the PCOS group than in the control group (52% vs. 10%). At the same time, it is was significant to find that one-fourth of patients in the PCOS group (24%) showed decreased T3 levels (compared to 0% in the control group). There was a significant

Table 1. Descriptive statistics for variables according to study group.

Variables	PCOS Mean±SD	Control Mean±SD	P value
Age (y)	18.0-40.0	19.0-36.0	
	27.7 ± 4.7	26.8 ± 4.7	0.439
BMI (Kg/m ²)	20.6-45.8	20.2-31.9	
	28.6 ± 4.0	24.9 ± 3.0	<0.001
LH mIU/ml	2.3-68.9	2.8-7.8	
	15.2 ± 11.1	4.7 ± 1.4	<0.001
FSH mIU/ml	1.3-90.0	3.1-8.2	
	9.2 ± 13.7	5.2 ± 1.3	0.007
TSH µIU/L	0.4-5.8	0.5-20.0	
	3.9 ± 1.3	3.1 ± 4.1	<0.001
T3 nmol/L	0.9-12.9	1.4-3.0	
	2.3 ± 1.7	2.2 ± 0.5	0.958
T4 nm/L	40.0-180.0	60.0-150.0	
	89.1 ± 34.5	90.6 ± 28.1	0.576

PCOS, polycystic ovarian syndrome; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; BMI, body mass index; T3, triiodothyronine hormone; T4, thyroxine hormone.

Table 2. Descriptive statistics for E2, AMH & fertility duration in polycystic ovarian syndrome (PCOS) group.

Variable	Min-Max	Mean± SD
Estradiol Pg/ml	10.0-183.1	68.7 ± 35.0
AMH pmol/L	0.6-6.9	3.3 ± 1.4
Duration of infertility (y)	1.0-13.0	4.1 ± 3.1

E2, Estradiol; AMH, Anti-Mullerian Hormone.

and direct correlation between age and T4 level, with increase in age being associated with a coefficient of increase of 0.238 in T4 level. This association was significant only in the PCOS group, in which increase in age was associated with a coefficient of increase of 0.294 per year in T4 level (P-value <0.001), (Table 3). Thyroid function parameters (TSH, T3, and T4 levels) were not correlated with BMI or LH or FSH level. Among the 50 patients with PCOS, 20 (40.4%) had subclinical hypothyroidism (SCH) and 30 (59.6%) were euthyroid (P-values <0.003 , <0.001), (Table 4).

Discussion

PCOS is the most common disorder among young women and an important cause of infertility in this age group. PCOS and thyroid disorder are two of the most common endocrine disorders in women, and while these conditions are very different. Hypothyroidism, is more common in women with PCOS than in the general population. Thyroid and PCOS are interconnected by both genetic and environmental factors which are believed

Table 3. Distribution of women according to study group, weight categories and to thyroid hormone parameters.

Variable	PCO		Control		P value
	N=50	100%	N=20	100%	
Weight					0.003
Normal Weight	7	14.0%	10	50.0%	
Overweight	28	56.0%	9	45.0%	
Obese	15	30.0%	1	5.0%	
TSH Level					0.001
Normal	24	48.0%	18	90.0%	
Elevated	26	52.0%	2	10.0%	
Decreased	0	0.0%	0	0.0%	
T3 Level					0.016
Normal	34	68.0%	20	100.0%	
Decreased	12	24.0%	0	0.0%	
Elevated	4	8.0%	0	0.0%	
T4 level					0.074
Normal	39	78.0%	20	100.0%	
Decreased	9	18.0%	0	0.0%	
Elevated	2	4.0%	0	0.0%	

PCO, polycystic ovaries; TSH, thyroid-stimulating hormone; T3, triiodothyronine hormone; and T4, thyroxine hormone.

to be contributing to thyroid disorders in PCOS, and is known to cause PCOS-like ovaries and overall worsening of PCOS and insulin resistance.

The most obvious connection between thyroid diseases and PCOS seem to be an increase in BMI, which is very prevalent in women with PCOS, observed than control group, (BMI for PCOS =28.6±4.0; BMI for control= 24.9±3.0 with P-value=<0.001).

In the present study, 20 (40%) of 50 patients with PCOS showed SCH. In a previous study, Michalakis *et al.* reported an SCH prevalence of 23% among patients seeking treatment for infertility, while another study reported a prevalence of 17.5% among patients with PCOS¹⁴.

A few studies have previously analyzed the prevalence of SCH in subjects with PCOS. Subclinical hypothyroidism is observed among women with PCOS, with an estimated prevalence range of 10–25%⁹. Regarding the impact of subclinical hypothyroidism on the clinical, hormonal or metabolism of women with PCOS, a recent meta-analysis has shown that the coexistence of SCH and PCOS leads to mild alterations in serum lipids, but not in hormone levels (TSH, FSH, LH and their ratio)⁹.

The findings of the present study are similar to those of a study by Enzevaei *et al.* in Iran, where 25.5% of subjects with PCOS were found to have SCH¹⁵. Similarly, in a study by Sinha *et al.*

Table 4. Correlations between thyroid hormone parameters in each studied group.

Variables	Sample		TSH microIU/L	T3 nmol/L	T4 nm/L
Age (y)	PCOS	r	-0.075	0.007	0.294
		P	0.607	0.963	0.039
	Control	r	-0.166	-0.402	0.078
		P	0.485	0.079	0.744
	All	r	-0.092	-0.030	0.238
		P	0.451	0.804	0.047
BMI (Kg/m2)	PCOS	r	-0.053	0.202	0.178
		P	0.715	0.160	0.217
	Control	r	-0.077	0.088	-0.428
		P	0.747	0.713	0.060
	All	r	0.014	0.187	0.049
		P	0.909	0.120	0.688
LH mIU/ml	PCOS	r	0.057	0.013	-0.075
		P	0.692	0.926	0.605
	Control	r	-0.292	-0.314	-0.112
		P	0.211	0.178	0.639
	All	r	0.070	0.027	-0.072
		P	0.565	0.827	0.554
FSH mIU/ml	PCOS	r	0.087	-0.025	-0.134
		P	0.547	0.862	0.355
	Control	r	0.099	-0.362	0.226
		P	0.678	0.117	0.338
	All	r	0.066	-0.022	-0.115
		P	0.586	0.859	0.344

PCOS, poly cystic ovary syndrome; TSH, thyroid-stimulating hormone; T3, triiodothyronine hormone; and T4, thyroxine hormone.

in India, 22.5% subjects with PCOS were reported to have SCH compared to 8.75% in controls and thyroid antibodies have been shown to be present in 27% of patients with PCOS versus 8% in controls¹⁶, also indicated the presence of elevated—T3, T4, TSH in patients with PCOS¹⁷. Kachuei *et al.* have also reported a significantly higher prevalence of anti-thyroglobulin antibodies in subjects with PCOS than in control subjects in an Iranian population¹⁸.

Examination and radiology investigations alone is not a reliable test to determine PCOS. TSH measures, T4, and T3 may be more applicable in the diagnosis of PCOS. Relying the combinations of all these is sufficient to make an accurate diagnosis and reason why so many people with PCOS and hypothyroid are not misdiagnosed.

Conclusion

We conclude that most patient with PCOS will have some degree of thyroid dysfunction, especially SCH. PCOS is much

more than just oligomenorrhea, amenorrhea, or infertility. Doctors must be aware of the risk factors for PCOS and intervene with a preventive approach, which may restore normal menstrual function, ovulation, and fertility. Therefore, physicians should consider screening for thyroid function tests at PCOS diagnosis, even in the absence of symptoms related with thyroid dysfunction.

Data availability

Underlying data

Zenodo: Thyroid hormonal changes among women with polycystic ovarian syndrome in Baghdad. <http://doi.org/10.5281/zenodo.2589282>¹³

This project contains the following underlying data:

- Thyroid and PCOS.xlsx (raw thyroid hormone levels for cases and controls)

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Grant information

The author(s) declared that no grants were involved in supporting this work.

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In the article, Mayada et al. compared the thyroid hormone profile and other clinical & biochemical parameters of women diagnosed as PCOS with non-PCOS otherwise healthy counterparts. In general, there is a scope of improvement in this article as it is not so well written.

I want to leave the following comments:

The term 'polycystic ovary syndrome' is preferred over 'polycystic ovarian syndrome'.

Abstract:

- 'The prevalence of polycystic ovaries on ultrasound is around quarter of all women but is not associated with the full syndrome'- is irrelevant here.
- This is not a case-control study, rather a cross-sectional study that involved a comparison group.
- In the result, the comparison of different hormone levels and BMI was done. But, in conclusion, you have commented about the prevalence of thyroid disorders in the two groups.

Introduction:

- The description of the pathophysiological link between PCOS and thyroid disorders is clumsy.

Methods:

- Cross-sectional study, not case-control.
- The sample size is small. How the sample size was calculated?
- The inclusion and exclusion criteria are not clearly defined. Was the PCOS cases treatment naïve?

- The age of the study participants was not mentioned in the method section. The age range of the subjects mentioned in the abstract (13-45 years) is dissimilar to that mentioned in Table 1.
- According to methodology, TVS was done in all cases. Is it justified for adolescents or sexually inactive (i.e. unmarried in your culture) women?
- The inclusion criteria do not match with the Rotterdam criteria mentioned in the guidelines.
- All PCOS women are not overweight and obese, many of them have normal even low BMI. Why were subjects with normal or low BMI were excluded? Again, patients of these categories are included in the tables. This is confusing.
- Hyperthyroidism or hypothyroidism are in the exclusion criteria but subjects with normal or low TSH, T4, and T3 are in the tables. Please explain.
- 'Good performance status', what does it mean?
- Avoid the confusing and vague terms like 'Positive past-medical history', 'Positive past-surgical history.' Specify the inclusion and exclusion criteria for both groups.
- The blood collection procedures are not written in detailed. Please mention the methods for the estimation of each hormone.
- Please mention the time of sample collection with respect to the phase of the menstrual cycle and fasting status.
- Free T4 and Free T3 were measured according to the method section. But in the tables and result section, you have written T4 and T3. Please explain.
- The measurement of anti-Mullerian Hormone is not mentioned in the method section though it is in the tables. Progesterone is measured according to the method section, it is not mentioned in the result or tables.
- SPSS is not appropriately written in the text, please see the website of the manufacturer for correct citation.

Results:

- The results are contradictory to the exclusion criteria of the PCOS subjects as I have already mentioned.
- Table 1: The ranges should be mentioned in the brackets with the mean values or may be mentioned in the separate columns. FSH is significantly different between the two groups ($p=0.007$).
- Table 2: Were all PCOS women infertile?
- Thyroid function status (euthyroid or subclinical hypothyroid) was not shown in any table, though in the result section it is written to be included in table 4.

- How many of the comparison group had thyroid dysfunction?
- Some suggestions about the presentation of the study result: a) compare all the demographic, clinical, and laboratory parameters between two groups; b) compare the subcategories of the study subjects according to thyroid status, biochemical hyperandrogenism, etc.

Discussion:

- The discussion section needs improvement.
- This part highlighted only the prevalence of SCH in PCOS and just compared the prevalence of this study with the others. There is no explanation regarding the higher prevalence of SCH in PCOS. Anti-thyroid antibodies were not measured in this study though previous findings of thyroid autoimmunity in PCOS were discussed.
- 'TSH measures, T4, and T3 may be more applicable in the diagnosis of PCOS.'- I failed to understand this. Thyroid function tests are mandatory to exclude thyroid dysfunctions which sometimes mimic PCOS clinically and radiologically, these are not used to diagnose PCOS.

Conclusion:

- In the study 60% of the PCOS women were euthyroid, but the authors concluded as 'most patient with PCOS will have some degree of thyroid dysfunction, especially SCH', which is not a reflection of the study result.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Endocrine disorders, Diabetes mellitus

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 24 June 2020

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Thank you to give me the opportunity to review, and comment on the article entitled (Thyroid hormonal changes among women with polycystic ovarian syndrome in Baghdad - a case-control study) published by Moustafa et al.

The article discussing an interesting subject, and aimed to assess the status of thyroid disorders in polycystic ovarian syndrome (PCOS).

Moustafa et al., stated in the introduction section that the global prevalence of polycystic ovaries among women is 25%¹. While, others mentioned that the PCOS affects 15-20% of women when the ESHRE/ASRM diagnostic criteria used².

Moustafa et al., mentioned that PCOS is a state of insulin resistance, which is considered to be the main factor contributing to development of the syndrome; diagnosis is based on the presence of two out of three of the following: clinical and/or biochemical androgen excess, anovulation and polycystic ovaries on pelvic ultrasound³.

While, other authors mentioned that PCOS has a reproductive manifestations (anovulation, and hyperandrogenism), and adverse metabolic outcome (insulin resistance (IR), and glucose intolerance)^{4,5}. So, IR is not a constant finding of PCOS, and it is only a manifestation of the PCOS with metabolic syndrome (MS). In addition, the PCOS should be diagnosed following the ESHRE/ASRM recommendation after exclusion of causes of hyperandrogenism such as late onset congenital adrenal hyperplasia (CAH), androgen secreting adrenal or ovarian tumors, and Cushing's syndrome^{4,5}.

So, Moustafa *et al.*, should include the late onset CAH, and Cushing's syndrome in their study

exclusion criteria.

Moustafa *et al.*, mentioned that hypothyroidism, is more common in women with PCOS than in the general population (40% of patients with PCOS showed sub-clinical hypothyroidism (SCH)). Also, they mentioned that the most obvious connection between thyroid diseases, and PCOS seem to be an increase in body mass index (BMI). Enzevaei *et al.* found that 25.5% of subjects with PCOS have SCH⁶. Similarly, Sinha *et al.* found that 22.5% subjects with PCOS were reported to have SCH⁷.

This can be explained by the high BMI of the PCOS-women, which produces relative thyroid hormone deficiency, and SCH. The non-diagnosed SCH of the PCOS-women converted to overt/clinical hypothyroidism with further increase in BMI. Consequently, the overt/clinical hypothyroidism, produces anovulation, and subsequent increased severity of PCOS⁹. This explains why Abdelazim and Kanshaiym, recommended screening of PCOS-women for the hypothyroidism⁹.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetrics, Gynecology and Reproductive medicine

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 10 December 2019

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In this paper Mayada et al. analyzed the prevalence of thyroid disorders in PCOS patients and controls prospectively enrolled at the Baghdad Teaching Hospital. The study included 70 women aged between 13 and 45 years old (50 PCOS patients and 20 controls) and for each of them an accurate personal and familiar history, details about menstrual cycle, symptoms of hyperandrogenemia and thyroid disorders were collected. Moreover, BMI was calculated and LH, FSH, TSH, T3 and T4 were measured.

The study has several points to be improved or better elucidated.

Major comments:

- The study is methodologically limited by the small number of enrolled patients, unclear and different inclusion/exclusion criteria for cases and controls, the total absence of normal values and inaccurate citation of literature on this item.

- In the introduction the pathophysiology of PCOS should be described in a clearer way, distinguishing between risk factors of PCOS and consequences of hyperinsulinemia. Both in abstract and introduction, PCOS diagnosis criteria must be clearly defined, according to Rotterdam criteria.
- Study design and setting: lines 9-10. The listed symptoms are not symptoms of thyroid dysfunction. Are the authors endocrinologists? I suggest to reconsider the whole study with colleagues more expert in gland function and alteration.
- Study design and setting, line 7: "last pregnancy". It is better to consider previous pregnancies and abortions.
- In order to have information about axis functionality, estrogen and progesterone should be measured too. Moreover, the authors should specify in which phase of the menstrual cycle (when cycle is present) blood test was performed. They have to give more methodological details: when the blood test was performed (morning? fasting?). Which methods were used to measure hormones in the lab? Normal ranges?
- Also FSH is significantly different among cases and controls.
- Table 1: please specify how values are expressed, mean? min-max? median? When min-max are reported, also median should be given. Indicate normal values.
- The authors state that TSH "was significantly greater" in PCOS subjects. What do they mean? Higher than what? Than controls? Than normal ranges?
- In table 3, there should be clearly defined criteria for "elevated" and "decreased". These are not scientific terms
- At the end of results, the authors wrongly refer to Table 4.
- Reference 9 is inappropriate.
- End of discussion: do the authors mean that thyroid hormones are useful in PCOS diagnosis? I completely disagree.
- Conclusions: It seems that if subclinical hypothyroidism is diagnosed and treated, PCOS is cured. It is a wrong message and not supported by data from the present study

Minor comments:

- Reference 2 is not correct. Please provide reference of the first published Rotterdam criteria.
- Introduction, line 9: "disruption" is not acceptable. Alterate function is better.
- "The genetic cause of high LH is unknown". In the AACE guidelines a possible explanation is suggested.

- End of introduction: "If it secretes hormones too fast". Too fast is not a scientific term, please rephrase.
- Free thyroid hormones were measured, thus the acronyms fT3 and fT4 should be used

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Thyroid, PCOS

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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