



Hypothyroidism A possible Risk Factor for Polycystic Ovary Syndrome among Jordanian Women

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Abstract

Women with PCOS demonstrate hormonal disturbances and serum lipid derangements. The aim of this study is to evaluate the possible existence, or any risk of hypothyroidism on PCOS among Jordanian women. Some serum hormones were measured with determination of serum lipid alterations as parameters in patients with PCOS, hypothyroidism, and compared with clinically health controls. The higher LH level observed in both PCOS and hypothyroidism as compared to control group with no statistically significant difference between them, and this could be attributed to higher androgen levels that desensitize the hypothalamus to the progesterone negative feedback regulation mechanism, also increased serum PRL was observed in PCOS, and was significant difference with hypothyroidism and control group, and (PROG) showed no alteration between all groups, while both (FSH) and (E2) showed significant difference among all groups but their values were in normal ranges and only (25 out of 42, 59.52%) patients with PCOS had SCH when TSH level range from ($> 6.5 \mu\text{IU/ml}$ and $< 10 \mu\text{IU/ml}$) as a hidden endocrine disturbance that may increases the PCOS risks and contribute enhances of some other dangerous diseases. Although, in the case of serum lipid's profiles, higher concentration of (TG) was observed in both PCOS and hypothyroidism groups with statistically significant deference, and the higher level of (T. CHOL and LDL) was noted between PCOS and hypothyroidism groups with no statistically significant difference between them, while both of which had significant difference with control group and no significant difference noted in HDL level between all groups at ($P > 0.05$).

1. Introduction

Hypothyroidism is a common clinical syndrome caused by a deficiency in thyroid hormones (thyroxine and tri-iodothyronine) High serum thyroid-stimulating hormone (TSH) levels are a clear indicator of primary hypothyroidism (Jayne ,*et al.*,2009)

Iodine deficiency is considered to be a main factor producing hypothyroidism; almost 50 milligrams of iodine are required each year for the formation of adequate quantities of thyroid hormones (Guyton and Hall ,2009) . Subclinical hypothyroidism (SCH), also called mild thyroid failure, is diagnosed when peripheral thyroid hormone levels are within normal range but serum TSH levels are elevated (between 5.0 and 9.0 mIU/L). This situation occurs in 3% to 8% of the general population.(Vanhab ,*et al.*,2009) SCH is more common among women than men, and its prevalence increases with age. Among patients with SCH, 80% have a serum TSH less than 10 mIU/L. The most important implication of SCH is high probability of progression to clinical hypothyroidism.(Vanhab ,*et al.*,2009) .

Hypothyroidism causes several metabolic disturbances, including decreased glucose removal, increased levels of sex hormone-binding globulin, weight gain, and hyperlipidemia (Seppel and Kosel .,1997; Rochon and Tauveron .,2003) . Hypothyroidism is also known to affect gonadal function, puberty, and fertility and may also lead to Polycystic ovary syndrome (PCOS) (Setian, 2007; Wagner .,2009) . PCOS, a common and heterogeneous disorder, is characterized by oligoanovulation, menstrual disturbances, and androgen excess (Rochon and Tauveron .,2003; Jayne .,2009) . PCOS affects approximately 5% to 10% of women of reproductive age (Knochenhauer .,1998 ; Asuncion .,2000) . Polycystic ovary syndrome is not only a reproductive problem but also represents a multifaceted, complex endocrine syndrome with important health implications (knochenhauer .,1998). Some cardiovascular risk factors associated with PCOS have been recognized in women at an early age. These factors are often connected with metabolic alterations, and include hypertension, endothelial dysfunction, dyslipidemia, and low grade chronic inflammation (Orio ,*et al.*,2008) The aim of this study was to identify associations between hypothyroidism and PCOS with respect to hormone levels and serum lipid profiles as an approach to assessing effects of hypothyroidism on PCOS.

2. Materials and Methods

2.1 Study design and methods

A Case-control study was conducted with 126 women in the age range of 20to 40 years. The women were divided into three groups: group I consisted of 42 patients with PCOS, group II consisted of 42 patients with hypothyroidism, and group III consisted of 42 healthy women used as controls. Serum hormone profiles for FT3, FT4, TSH, LH, FSH, prolactin, progesterone, and estradiol were determined, and serum lipid profiles for total cholesterol, triglyceride, HDL, and LDL were determined. Data acquired for the three groups (PCOS,

Hypothyroidism, and Control) were compared by one-way ANOVA, analysis of variance, and post hoc LSD test.

2.2 Sample collection and preservation

Samples were collected during July, August, and September, 2011 from patients seen at two different hospitals in two different Jordan governorates: Ibin Alnafis Hospital, which is located in the city of Irbid and Amal Hospital in Amman, the capital of Jordan. Whole blood samples (5 ml) were obtained from each patient, separated by centrifugation, and the serum stored at -70°C until being assayed in March 2012.

2.3 Assays

Hormones (FT3, FT4, TSH, FSH, E2, Prolactin, Progesterone, and LH) were assayed by ELISA (AWARENESS) using commercial kits in duplicate and according to supplier protocols (BIOCHECK, INC, 323 Vintage Park Dr., Foster City, CA 94404 USA), , and (Monobind Inc., Lake Forest, CA 92630 USA).. Serum lipid profiles were measured by electrochemiluminescence method using a Hitachi 902 (Tokyo, Japan).

2.4 Statistical Analysis

Hormone and lipid profile data (reported as mean \pm SD) among the three groups (PCOS, Hypothyroidism, and Control) were compared by one-way ANOVA, analysis of variance, and post hoc LSD test, using SPSS version 19.0. (Chicago, IL). Comparisons of continuous variables among group I, group II, and group III was done by analysis of variance, one-way ANOVA. Correlations between hormones and lipids within and between groups were determined.

3 Hormonal Profile Estimation

Hormone data are shown in Table 4.1. Statistical analysis of hormone profiles showed that there were significant differences in hormone profiles among the groups. The FT3 level was significantly different in the PCOS group compared with the hypothyroidism group ($P < 0.05$) (Table 4.1), whereas the FT3 level in the control group didn't show a significant difference with either of the other groups ($P > 0.05$).

The FT4 level of the hypothyroid group was significantly different from both the control group and PCOS group ($P < 0.05$). The control group and PCOS group did not exhibit any significant differences between them ($P > 0.05$) (Table 1).

Serum TSH level in the hypothyroidism group was significantly different from both the control group and the PCOS group. Serum TSH was not significantly different between the control group and PCOS group ($P > 0.05$) (Table 1).

Table 1: Hormone profiles of studied cases.

Serum Hormone	PCOS	Hypothyroidism	Control
FT3 (ng/ml)	1.60±0.74a*	0.64 ±0.17b	1.65 ±0.81ab
FT4 (ng/ml)	1.44±0.49a	0.50±0.10b	1.50±0.47a
TSH (μIU/ml)	6.82±1.32a	9..02±1.35b	6.00±1.786a
LH (mIU/ml)	53.19±7.3a	51.55±7.53a	45.79±6.92.b
FSH (mIU/ml)	18.77±5.20a	12.64±2.85a	10.73±3.36a
PRL (ng/ml)	38.81±6.8a	19.71±4.13b	18.82±3.89b
PROG (ng/ml)	8.37±1.67a	8.46±1.28a	8.82±0.96a
E2 (pg/ml)	176.31±7.37a	156.91±19.78a	87.44±29.46a

Data within the same row followed by similar letters are not significantly different ($p>0.05$) according to LSD; values are means±SD of 42 patients for each group. Results were analyzed by one way ANOVA using software package SPSS (Chicago, IL) version 19.

Serum LH in the control group was significantly different from both the hypothyroidism group and PCOS group, while there was no significant difference between hypothyroidism and PCOS groups ($P>0.05$).

Serum PRL in the PCOS group was significantly different from both the control and hypothyroidism groups. Serum PRL was not significantly different between the control group and hypothyroidism group ($P>0.05$) (Table 1).

Serum levels of FSH, PROG, and E2 were not significantly different between any groups ($P>0.05$) (Table 1).

The analysis of variances showed that there was a negative correlation between FT3 and E2 within the control group (-0.420, $P=0.001$), while there was no correlation between FT3 and all other tested hormones. A positive correlation between PROG and FT4 was noted (0.434, $P<0.01$) in the control group. No correlation (positive or negative) was found between any other pair of hormones in the control group.

Analysis of hormone levels in the hypothyroidism group indicated a negative correlation of FT3 with PROG (-0.648, $P<0.01$). No correlation was found between any other pair of hormones in the hypothyroidism group.

A negative correlation between FT4 and FSH (-0.520 at $P<0.01$) was found in the PCOS group. No correlation was found between any other pair of hormones in the PCOS group.

4. Lipid profile estimation

Lipid profiles were determined for all studied cases (Control, Hypothyroidism, and PCOS groups) (Table 2). The mean total cholesterol in the control group was significantly different from mean total cholesterol in both hypothyroidism and PCOS groups ($P<0.05$).

There was no significant difference in mean total cholesterol between the hypothyroidism and PCOS groups ($P>0.05$).

Mean serum HDL was not significantly different between any of the groups ($P>0.05$) (Table 4.2). As well, there was no significant difference in mean serum LDL between the hypothyroidism and PCOS groups; however, the control group showed a significant difference with both the hypothyroidism group and the PCOS group ($P<0.05$). Mean serum TG was significantly different among all three groups ($P<0.05$) (Table 2).

Table 2: Serum Lipid profiles (total cholesterol, TG, HDL, and LDL) for all studied cases (Control, Hypothyroidism and PCOS).

serum lipid profile	PCOS	Hypothyroidism	Control
	mg/dl (mean \pm SD)		
Total cholesterol	228.73 \pm 39.93a	240.09 \pm 42.65a	159.50 \pm 21.59b
TG	228.83 \pm 86.05c	161.57 \pm 37.32b	118.16 \pm 24.28a
HDL	37.31 \pm 6.85a	37.90 \pm 8.88a	39.41 \pm 6.33a
LDL	157.11 \pm 34.11a	166.17 \pm 42.90a	96.15 \pm 96.15b

Lipid profile (mean \pm SD) was estimated by electrochemiluminescence on a Hitachi machine (902). Data within the same row followed by similar letters are not significantly different ($p>0.05$) according to LSD; values are means of 42 sample for each case; Results were analyzed by one ways ANOVA using SPSS version 19.

In the control group, analysis of variances for lipid profiles identified a positive correlation between total cholesterol and LDL (0.946, $P=0.01$), a positive correlation between TG and HDL (0.417, $P=0.01$), and a negative correlation between HDL and LDL (-0.344, $P=0.02$).

In the hypothyroidism group, analysis of variances for lipid profiles identified a positive correlation between total cholesterol and both TG (0.431, $P=0.004$) and LDL (0.989, $P=0.000$), and a negative correlation with HDL (-0.695, $P=0.000$). A positive correlation was identified between TG and both total cholesterol (0.413, $P=0.004$) and LDL (0.467, $P=0.002$), and a negative correlation between TG and HDL (-0.498, $P=0.002$).

In the PCOS group analysis of variances for lipid profiles identified a positive correlation between total cholesterol and both TG (0.320, $P=0.039$) and LDL (0.980, $P=0.000$). A positive correlation was identified between TG and LDL (0.359, $P=0.020$), but HDL didn't show a correlation with any tested lipid

Table 3. Illustrates percentile rates of hypothyroidism, SCH, and PCOS cases among hypothyroidism group and PCOS group depending on the higher TSH values with lower FT4, mild elevated TSH with normal FT4 and FT3, and higher levels of LH and PRL altogether for hypothyroidism, SCH, and PCOS

parameters (total cholesterol, TG, or LDL).

Table 3. Comparative description of percentile rates of the cases between Hypothyroidism and PCOS		
Cases	Hypothyroidism	PCOS
	78.57% (33 out of 42)	9.52% (4 out of 42)
SCH	23.8% (10 out of 42)	59.52% (25 out of 42)
PCOS	26.2% (11 out of 42)	52.38% (22 out of 42)
<p>PCOS; depending on both high levels of LH and PRL altogether</p> <ul style="list-style-type: none"> • SCH; depending on mild elevate TSH with normal FT4 and FT3. • Hypothyroidism; depending on high TSH and low FT4 values according to the normal ranges. 		

5. Discussion

For many decades, an important subject in the fields of gynecology and endocrinology has been the correlation between polycystic ovary syndrome and hypothyroidism among women. Primary hypothyroidism is the most common pathological hormone deficiency, having an incidence as high as 4.3% (Roberts & Landenson, 2004). Deficiencies of thyroid hormones produces many consequent end-organ effects, including effects in the female reproductive system. Hypothyroidism can interfere with gonadotropin secretion by increasing serum prolactin levels (Blackwell & Chang, 1986). Clinical manifestations, including menstrual irregularities and/or luteal phase defects may occur during this disease (Krassas, 2000)

On the other hand, it is not easy to provide a uniform definition of PCOS because of the great variety of different phenotypes that occur (Strowitzki, *et al.*, 2010). Application of the Rotterdam criteria increases the frequency of diagnosis of PCOS as mentioned in numerous publications (Strowitzki, *et al.*, 2010). As a result, examination of simple clinical parameters such as serum hormones and lipid profiles may permit an evaluation of PCOS in routine practice. In this study, we found that ovarian dysfunction, represented by clinical parameters of PCOS, are associated with hormonal disturbances. In particular, we intended to evaluate simple hormonal parameters and lipids to evaluate their utility as screening tools in PCOS. In this regard, we choose to evaluate hypothyroidism as a rough surrogate parameter.

Our study included three groups of women: patients with PCOS, hypothyroid patients, and healthy controls. Each group included forty two women. We assessed a possible association

between hypothyroidism and PCOS in comparison with the healthy control group. We found alterations in some serum hormones and serum lipid profiles indicating occurrence of similar metabolic disturbances between hypothyroidism and PCOS.

TSH and FT4 levels are useful indicators for both subclinical and overt hypothyroidism (Sawin, *et al.*, 1985). The results of this study showed that the mean TSH level in the hypothyroidism group was significantly different from the PCOS group. TSH levels in the control group were significantly different from TSH of the hypothyroidism group, but was not significantly different from the PCOS group, although TSH levels were increased in both the hypothyroidism and PCOS groups compared to the control group. Mohd, *et al.*, 2011 demonstrated that TSH was elevated in both subclinical hypothyroidism and polycystic ovary syndrome. Our results agree with this study, and using the specific definition of subclinical hypothyroidism, we determined that 42.85% of patients exhibiting subclinical hypothyroidism were found in the PCOS group.

Serum LH levels in our comparative study demonstrated no significant difference between PCOS and hypothyroidism, but LH was significantly higher in both groups than in the control group. Taylor, *et al.*, 1988 found that plasma LH levels are raised in a great number of women with PCOS. Waldstreicher, *et al.*, 1988 determined that the increased rate and amplitude of LH pulses is a consequence of a persistent, rapid frequency of secretion of endogenous gonadotropin releasing hormone (GnRH). Marshall, *et al.*, 2001 showed that anovulation in women with PCOS is due to the persistent, rapid frequency of GnRH stimulation of the pituitary gland that results in elevated LH and testosterone levels, low FSH levels, and abnormal follicular maturation.

Although large differences in mean FSH levels were found, these were not significantly different between any groups. Similar results were obtained for estradiol and progesterone between all groups. Our results agree with Greydanus, *et al.*, 2009, who observed that when puberty begins, the anterior pituitary gland reacts to increased estrogen levels by increasing LH concentrations and reducing FSH production, which causes irregular stimulation of ovarian-derived estradiol and androgens as well as abnormal maturation of ovarian follicles and a state of chronic anovulation. Estradiol levels can be slightly raised or normal in PCOS patients and in patients with other hyperandrogenism conditions. Gosh, *et al.*, 1993 found that increasing estradiol is among hormonal changes associated with overt hypothyroidism. Our results regarding estradiol disagree with Gosh *et al.* in that we found a negative effect between free tri-iodothyronine and estradiol in the control group.

With regard to prolactin levels, we found significant differences between PCOS and hypothyroidism groups, but no significant difference between hypothyroidism and control groups. Ghosh *et al.*, 1993 also reported that one of the hormonal disturbances associated with overt hypothyroidism is increasing prolactin, which is consistent with our study. Asuncion, *et al.*, 2000 demonstrated that moderate increases in serum PRL levels are often found in women with hyperandrogenism, and may also result from the stress of blood sampling and from treatment with oral contraceptives.

We found increased total cholesterol in both hypothyroidism and PCOS groups, but the differences were not significant. However, differences in total cholesterol were significant

between both hypothyroidism and PCOS groups compared with the control group. Serum TG results were similar to total cholesterol results, but the differences were significant between all pairs of groups. Mean HDL levels were similar among all groups, and were not significantly different.

Many studies have identified variations in cholesterol, TG, and LDL in patients with subclinical hypothyroidism, but the results are not consistent. Tuzcu et al., in a recent study, found increased total cholesterol and LDL in patients with subclinical hypothyroidism without any change in TG or HDL compared with controls. Al Sayed, *et al.*, 2006 observed similar results in Kuwaiti women. In the present study, increased LDL concentrations were noted with increasing total cholesterol in both hypothyroidism and PCOS groups, and differences between them were not significant statistically. However, differences were significant between either hypothyroidism or PCOS group as compared with the control group. In contrast, Brenta, *et al.*, 2007 recently found that there was no change in lipid levels among patients with subclinical hypothyroidism compared with controls. A recent study by Mueller, *et al.*, 2009 did not reveal any alterations in levels of total cholesterol, TG, or LDL among euthyroid PCOS subjects who were stratified on the basis of a TSH cutoff of 2 IU/L. Whether hypothyroidism alters the phenotypic expression of PCOS, and whether subclinical hypothyroidism has any effect on PCOS in these patients is not apparent. In our study, we did not measure clinical or biochemical parameters for comparing between groups, but we found differences and similarities in hormone and lipid parameters between groups. Based on our results, we conclude that, except for minor changes in lipid profile, PCOS is not altered in the presence of subclinical hypothyroidism.

Although the relationship between PCOS and hypothyroidism has been well studied, with few exceptions, similar effects of subclinical hypothyroidism on different clinical and metabolic parameters have not been found (Ghosh, *et al.*, 1993).

However, the clinical pictures of hypothyroidism and PCOS are easy to confuse, and therefore, the present results should be applied only to patients in whom hypothyroidism and PCOS might coexist. In this situation, our results are consistent with previous results of Ghosh, *et al.*, 1993. Consequently, further studies on the relationship between hypothyroidism and PCOS are needed; there may be an interaction between them as our results suggest.

Our results show that subclinical hypothyroidism is prevalent among women with polycystic ovary syndrome. We hypothesize that hypothyroidism as a risk factor for PCOS. This is supported by Iptisam, *et al.*, 2010 who suggested that the PCOS-like form of the ovaries can be caused by hypothyroidism.

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References

- Al Sayed A., Al Ali N., Bo Abbas Y., Alfadhli E., Subclinical hypothyroidism is associated with early insulin resistance in Kuwaiti women. *Endocr J* (53) (2006) 653–7.
- Asuncion M., Rosa M., Calvo José L., San Millán, José Sancho, Sergio Avila and Héctor F., Escobar-Morreale, A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *The Journal of Clinical Endocrinology and Metabolism*. (85) (2000) 2434–2438.
- Blackwell RE., Chang RJ., Report of the National Symposium on the clinical Management of Prolactin-Related Reproductive Disorders, *Fertil Steril*, (45) (1986) 607-10.
- Brenta G., Berg G., Arias P., Zago V., Schnitman M., Muzzio ML., Lipoprotein alterations, hepatic lipase activity, and insulin sensitivity in subclinical hypothyroidism: response to L-T4 treatment, *Thyroid* (17) (2007) 453–60.
- Ghosh S., Kabir S. N., Pakrashi A., Siddhartha C., Subclinical hypothyroidism: a determinant of polycystic ovary syndrome, *Horm Res*. (39) (1993) 61–66.
- Greydanus, Donald E., Hatim A. Omar, Artemis K. Tsitsika, and Dilip R. Patel, Menstrual Disorders in Adolescent Females: Current Concepts. *Dis Mon* (55) (2009) 45-113.
- Guyton & Hall, Textbook of Medical Physiology, 12th Edition, John Hall., (2011), p. 917.
- Iptisam Ipek Muderris, Abdullah Boztosum, Gokalp Oner, Fahri Bayram, Effect of thyroid hormone replacement therapy on ovarian volume and androgen hormones in patients with untreated primary hypothyroidism, *Ann Saudi Med* 31(2) (2011) 145- 151.
- Jayne A Franklyn., Hypothyroidism, Elsevier Ltd. *MEDICINE*, (2009) **37**: 8 p. 426-429.
- Knochenhauer E.S., T. J. Key, M., Kahsar-Miller, W. Waggoner, L. R., Boots and R. Azziz., Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study, *The Journal of Clinical Endocrinology and Metabolism* (83) (1998) 3078–3082.
- Krassas G., Thyroid disease and female reproduction, *Fertil Steril*, (74) (2000) 1063 -70.
- Marshall JC., Eagleson CA., McCartney CR., Hypothalamic dysfunction, *Mol Cell Endocrinol* (183) (2001) 29–32.
- Mohd Ashraf Ganie., Bashir Ahmad Laway., Tariq Ahmed Wani., Mohd Afzal Zargar., Sobia Nisar., Feroze Ahamed., M. L., Khurana., and Sanjeed Ahmed., Association of subclinical hypothyroidism and phenotype, insulin resistance, and lipid parameters in young women with polycystic ovary syndrome, *j. fertnstert* (2011) 01.149.
- Mueller A., Schöfl C., Dittrich R., Cupisti S., Oppelt PG., Schild RL., Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome, *Hum Reprod* 24 (2009) 2924–30.
- Orio F., Vuolo L., Palomba S., Lombardi G., Colao A., Metabolic and cardiovascular consequences of polycystic ovary syndrome. *Minerva Ginecol* (16) (2008) (February (1)) 39—51.

- Roberts C. G., Landenson P. W., Hypothyroidism, *Lancet*. (363) (2004) 793-803.
- Rochon C., Tauveron I., Dejax C., Benoit P., Capitan P., Fabricio A., Response of glucose disposal to hyperinsulinemia in human hypothyroidism and hyperthyroidism, *Clin Sci (Lond)* (104) (2003) 7–15.
- Sawin CT., Castelli WP., Hershman JM., McNamara P., Bacharach P., The aging thyroid. Thyroid deficiency in the Framingham Study, *Arch Intern Med*, (145) (1985) 1386-8.
- Seppel T., Kosel A., Schlaghecke R., Bioelectrical impedance assessment of body composition in thyroid disease, *Eur J Endocrinol* (136) (1997) 493–8.
- Setian NS., Hypothyroidism in children: diagnosis and treatment, *J Pediatr (Rio J)* (83) (2007) S209–16.
- Strowitzki Thomas., Edison Capp., Helena von Eye Corleta., The degree of cycle irregularity correlates with the grade of endocrine and metabolic disorders in PCOS patients, *European Journal of Obstetrics & Gynecology and Reproductive Biology*, (149) (2010) 178–181.
- Taylor AE., McCourt B., Martin KA., Determinants of abnormal gonadotropins secretion in clinically defined women with polycystic ovary syndrome, *J Clin Endocrinol Metab* (82) (1997) 2248–56.
- Vanhab Fatourechi, MD., Subclinical Hypothyroidism: An Update for Primary Care Physicians, *Mayo Foundation for Medical Education and Research*. January; 84(1) (2009) 65-71.
- Wajner SM., Wagner MS., Maia AL., Clinical implications of altered thyroid status in male testicular function, *Arq Bras Endocrinol Metabol* (53) (2009) 976–82.
- Waldstreicher J., Santoro NF., Hall JE., Filicori M., Crowley WF. Jr., Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian disease: indirect evidence for partial gonadotroph desensitization, *J Clin Endocrinol Metab*, (66)(1988) 165-72.