Common endocrine disorders associated with the polycystic ovary syndrome

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Abstract

Introduction: Screening of polycystic ovary syndrome (PCOS) women for hypothyroidism and hyperprolactinemia was suggested, because the undiagnosed hypothyroidism and hyperprolactinemia can aggravate the PCOS symptoms.

Aim of the study: To determine whether the insulin resistance (IR), hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with the PCOS.

Material and methods: One hundred and twenty PCOS women were compared to 120 non-PCOS controls in this study. Participants’ day 2-3 hormonal profile and insulin resistance (IR) using the fasting glucose and fasting insulin were evaluated. Collected data were analyzed to determine whether the IR, hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with the PCOS.

Results: TSH and prolactin were significantly high in PCOS women (6.4 ±4.2 and 934 ±102.3, respectively) than controls (3.5 ±3.3 and 445 ±77.5 mIU/ml, respectively) (p = 0.004 and 0.001, respectively). The PCOS women had significantly high relative risk of IR (RR 3.0 (95% CI: 1.9-4.7) p < 0.0001), hypothyroidism (RR 3.4; 95% CI: 1.7-6.9) (p = 0.0005), and hyperprolactinemia (RR 3.15; 95% CI: 1.8-5.6) (p = 0.0001) than controls. The PCOS women had higher odds of IR (OR 4.8; 95% CI: 2.6-8.8) (p < 0.0001), hypothyroidism (OR 4.29; 95% CI: 1.9-9.4) (p = 0.0003), and hyperprolactinemia (OR 4.27; 95% CI: 2.1-8.5) (p < 0.0001) than controls.

Conclusions: TSH and prolactin were significantly high in studied PCOS women, and 47.5% of the studied PCOS women had IR. The PCOS women had significantly higher odds and relative risks of IR, hypothyroidism, and hyperprolactinemia than controls. IR, hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with PCOS.

Key words: endocrine, disorders, PCOS.

Introduction

Polycystic ovary syndrome (PCOS) affects 15-20% of women when the ESHRE/ASRM diagnostic criteria used [1]. PCOS has reproductive manifestations (anovulation, and hyperandrogenism), and adverse metabolic outcome (insulin resistance – IR and glucose intolerance) [1-3].

PCOS occurs following interaction of the genetic mutation with the hypothalamic-pituitary dysfunction [2]. An aromatase enzyme genetic mutation was suggested as a cause of PCOS in some studies [4-5], and a recent research showed that the PCOS women with CYP17 gene mutation had significantly higher total testosterone, and clinical features of hyperandrogenism than PCOS women with wild, and heterozygous genotype [6].

In addition, Kshetrimayum et al. suggest that the genetic/host, and the environmental/lifestyle factors might be related to the pathophysiology of PCOS after prenatal exposure to androgen [7]. Fifty-six percent (56%) of the PCOS women had evidence of hypothyroidism [8]. The elevated thyrotropin-releasing hormone (TRH) in hypothyroidism acts as dopamine antagonist with subsequent hyperprolactinemia [9]. Abdelazim and Kanshaiym recommended screening of PCOS women for the hypothyroidism, and hyperprolactinemia because the undiagnosed hypothyroidism, and hyperprolactinemia can aggravate the PCOS symptoms [10]. Therefore, this study designed to determine whether the IR, hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with the PCOS.
**Material and Methods**

One hundred and twenty (120) PCOS women were included in this prospective multicenter study and compared with 120 non-PCOS controls to determine whether the IR, hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with the PCOS.

Women with endocrine disorders (thyroid, adrenal, prolactin) received contraceptives pills, corticosteroids, or ovulation induction during last 6 months were excluded from this study.

Participants evaluated thoroughly to detect their body mass index (BMI), waist circumference (WC), and the ultrasound criteria of polycystic ovaries.

Participants’ day 2-3 hormonal profile (luteinizing hormone – LH, follicle stimulating hormone – FSH, thyroid stimulating hormone – TSH, prolactin, testosterone, androstenedione, 17-hydroxy(OH)progesterone, and dehydroepiandrosterone – DHEA) with fasting glucose and insulin were also evaluated. Any hormonal deviation from the normal range confirmed by a second laboratory result 8 weeks apart. Fasting glucose (G) divided by fasting insulin (I) to get the G/I ratio (G/I ratio < 4.5 is a useful screening for IR) [3].

The diagnosis of PCOS was based on the ESHRE/ASRM criteria [11]. The BMI calculated using the body weight divided by the square length (kg/m²) [2]. The WC measured between the upper margin of iliac crest, and lower costal margin (>35 inches means increased WC) [2].

The polycystic ovaries diagnosed by ultrasound following detection of ≥12 follicles in each ovary, each follicle measuring 2-9 mm and/or increased ovarian volume (>10 ml) according to the Rotterdam ESHRE/ASRM criteria [11].

However, Teede et al. mentioned that the threshold for polycystic ovarian morphology (PCOM) using the endo-vaginal ultrasound transducers of 8 MHz frequency is ≥20 follicles per ovary and/or an ovarian volume ≥10 ml on either ovary, ensuring that there are no corpora lutea, cysts or dominant follicles [12].

Participants with prolactin level double the normal value (normal < 614 mIU/ml) evaluated for pituitary adenoma using magnetic resonance imaging (MRI).

Causes of excess androgen such as congenital adrenal hyperplasia (late onset), androgen secreting tumors, and Cushing’s syndrome were excluded before diagnosing PCOS according to the ESHRE/ASRM recommendation [11].

Collected data were analyzed to determine whether the IR, hypothyroidism and hyperprolactinemia are common endocrine disorders associated with the PCOS.

**Sample size**

The sample size calculated using the G Power software version 3.17. An effective sample include > 220 women in two groups (110 PCOS women, and 110 controls) needed to produce a statistically acceptable figure.

**Statistical analysis**

Collected data were analyzed using the Statistical Package for Social Science (SPSS) version 23, (Chicago, IL, USA). The Chi-square (X²), and Student t-test used to compare the qualitative, and quantitative variables, respectively. Logistic regression analysis used to calculate the relative risk (RR), and Odds ratio (OR) of IR, hypothyroidism, and hyperprolactinemia in PCOS women. The p value < 0.05 was considered significant.

**Results**

One hundred and twenty PCOS women compared with 120 non-PCOS controls in this study to determine whether the IR, hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with the PCOS.

The BMI, LH, and LH/FSH ratio were statistically high in the studied PCOS-women (31.5 ±5.2, 16.3 ±5.7 and 2.3 ±3.7, respectively) than controls (25.5 ±4.1 kg/m², 6.1 ±4.3 mIU/ml and 1.05 ±2.9; respectively), (p = 0.005, 0.001 and 0.004; respectively). TSH, and prolactin were significantly high in the studied PCOS women (6.4 ±4.2

| Variable | PCOS women (study group) (n =120) | Non-PCOS controls (n =120) | p-value (95% CI) |
|----------|----------------------------------|---------------------------|-----------------|
| Age (years) | 22.4 ±5.1 | 24.6 ±6.3 | 0.9 (~3.65, 2.2, 0.74) |
| BMI (kg/m²) | 31.5 ±5.2 | 25.5 ±4.1 | 0.005* (4.8, 6, 7.2) |
| FSH (mIU/ml) | 7.2 ±6.1 | 6.4 ±5.6 | 0.18 (~0.69, 0.8, 2.29) |
| LH (mIU/ml) | 16.3 ±5.7 | 6.1 ±4.3 | 0.001* (8.9, 10.2, 11.48) |
| LH/FSH ratio | 2.3 ±3.7 | 1.05 ±2.9 | 0.004* (0.4, 1.25, 2.1) |
| TSH (mIU/ml) | 6.4 ±4.2 | 3.5 ±3.3 | 0.004* (1.9, 2.9, 3.9) |
| Prolactin (mIU/ml) | 934 ±102.3 | 445 ±77.5 | 0.001* (465.7, 489, 512.3) |

PCOS – polycystic ovary syndrome, FSH – follicle stimulating hormone, LH – luteinizing hormone, TSH – thyroid stimulating hormone, CI – confidence interval, * significant difference. Student t-test used for statistical analysis. Data presented as mean ±standard deviation (SD)
The rates of overweight, and obesity were significantly high in the studied PCOS group (42.5% and 39.17%; respectively) than controls (21.7% and 15.8%; respectively), \( p = 0.01 \) and \( 0.002; \) respectively. 44.17% of the studied PCOS women had WC >35 inches compared to 19.17% of the controls \( p = 0.002 \), and 47.5% of the studied PCOS women had IR compared to 15.8% of the controls \( p < 0.0001 \) than controls. The studied PCOS women had also significantly high RR of hypothyroidism (RR 3.4 (95% CI; 1.7-6.9); \( p = 0.0005 \), and hyperprolactinemia (RR 3.15 (95% CI; 1.8-5.6); \( p = 0.0001 \)) than controls (Table 3).

The studied PCOS women had significantly high RR of overweight (OR 2.67 (95% CI; 1.85-6.3); \( p = 0.0001 \), obesity (OR 3.4 (95% CI; 1.85-6.3); \( p = 0.0001 \), WC > 35 inches (OR 3.3 (95% CI; 2.6-8.8); \( p < 0.0001 \)) than controls. The studied PCOS women had also significantly higher odds of hypothyroidism (OR 4.27 (95% CI; 2.1-8.5); \( p < 0.0001 \), and hyperprolactinemia (OR 4.27 (95% CI; 2.1-8.5); \( p < 0.0001 \)) than controls (Table 4).

### Discussion

Fifty-six percent (56%) of the PCOS women had evidence of hypothyroidism [8]. The elevated thyrotropin-releasing hormone (TRH) in hypothyroidism acts as dopamine antagonist with subsequent hyperprolactinemia [9]. Therefore, one hundred and twenty PCOS women compared with 120 non-PCOS controls in this study had significantly high RR of hypothyroidism (RR 3.4 (95% CI; 1.7-6.9); \( p = 0.0005 \), and hyperprolactinemia (RR 3.15 (95% CI; 1.8-5.6); \( p = 0.0001 \)) than controls (Table 3).

| Variable | PCOS women (study group) (n = 120) | Non-PCOS controls (n = 120) | Relative risk (95% CI); \( p \)-value |
|----------|----------------------------------|----------------------------|-----------------------------------|
| BMI 25-29.9 kg/m² | 42.5 (51/120) | 21.7 (26/120) | 1.96 (1.3-2.9); 0.0009* |
| BMI ≥ 30 kg/m² | 39.17 (47/120) | 15.8 (19/120) | 2.4 (1.54-3.9); 0.0002* |
| WC > 35 inches | 44.17 (53/120) | 19.17 (23/120) | 2.3 (1.5-3.5); 0.0001* |
| Glucose/insulin ratio < 4.5 | 25.8 (31/120) | 7.5 (9/120) | 3.0 (1.9-4.7); < 0.0001* |
| PCOS – polycystic ovary syndrome, WC – waist circumference, G/I – glucose/insulin, TSH – thyroid stimulating hormone, CI – confidence interval. * significant difference. Data presented as number and percentage (%) |
study to determine whether the IR, hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with the PCOS.

The odds, and RR of overweight, obesity, and WC > 35 inches were significantly high in the studied PCOS women than controls. 44.17% of the studied PCOS women had WC > 35 inches compared to 19.17% of the controls (\(p = 0.002\)). Abufaza et al. reported that the PCOS obesity characterized by WC > 35 inches [2].

About 47.5% of the studied PCOS women had IR compared to 15.8% of the controls (\(p = 0.0001\)), and the studied PCOS women had significant higher odds, and RR of IR (OR 4.8; RR 3.0) than controls. IR means decreased glucose response to insulin with subsequent hyperinsulinemia, and utilization of fat as a source of energy (lipolysis), which leads to elevated triglyceride, and decreased HDL-cholesterol, glucose intolerance, and cardiovascular risks [1-3]. Insulin stimulates ovarian androgen production through its direct effect on the LH receptors of the theca cells with subsequent hyperandrogenism which interferes with ovarian follicle maturation with subsequent anovulation [13].

This explains the relation between hyperinsulinemia, and both hirsutism, and anovulation in PCOS [14]. A positive relation between hyperinsulinemia, and the number of the ovarian follicles reported by Sikka et al. in PCOS women [13].

Mostafa et al. found that about 46% of PCOS Egyptian women had IR [3]. They also found the hirsutism was significantly high in IR PCOS women compared to non-IR PCOS controls, and they suggested the use of the G/I ratio as a useful screening test for IR in PCOS women [3].

Although, Cho et al. found that the LH/FSH ratio has little use in diagnosing PCOS [15]. The LH, and the LH/FSH ratio were statistically high in the studied PCOS women than controls. In addition, Nath et al. [8] and Banaszewska et al. [16] also reported an elevated LH/FSH ratio in PCOS women.

Recently, Dapas et al. defined 2 distinct PCOS subtypes: a “reproductive” PCOS group, characterized by higher LH, and sex hormone binding globulin (SHBG) levels with relatively low BMI, and insulin levels, and a “metabolic” PCOS group, characterized by higher BMI, glucose, and insulin levels with lower SHBG, and LH levels [17].

The TSH, and prolactin were significantly high in the studied PCOS women than controls (\(p = 0.004\) and 0.001; respectively), 25.8% of the studied PCOS women had elevated TSH compared to 7.5% of the controls, and 34.17% of the studied PCOS women had hyperprolactinemia compared to 10.8% of the controls. The studied PCOS women had also significant higher odds, and RR of hypothyroidism (OR 4.29; RR 3.4), and hyperprolactinaemia (OR 4.27; RR 3.15) than controls. The high BMI of the PCOS women produces relative thyroid hormone deficiency (sub-clinical hypothyroidism (SCH)). The non-diagnosed SCH of the PCOS women converted to overt hypothyroidism with further increase in BMI. Consequently, the overt hypothyroidism, produces anovulation, and increased severity of PCOS symptoms [8].

Enzevaei et al. found that 25.5% of the PCOS subjects have SCH [18]. Similarly, Sinha et al. reported that 22.5% of the PCOS women had elevated TSH compared to 7.5% of the controls, and 34.17% of the studied PCOS women had hyperprolactinemia compared to 10.8% of the controls. The studied PCOS women had also significant higher odds, and RR of hypothyroidism (OR 4.29; RR 3.4), and hyperprolactinaemia (OR 4.27; RR 3.15) than controls.

The high BMI of the PCOS women produces relative thyroid hormone deficiency (sub-clinical hypothyroidism (SCH)). The non-diagnosed SCH of the PCOS women converted to overt hypothyroidism with further increase in BMI. Consequently, the overt hypothyroidism, produces anovulation, and increased severity of PCOS symptoms [8].

The data presented in Table 4 shows the odds ratio (OR) of overweight, obesity, insulin resistance (IR), hypothyroidism, and hyperprolactinemia in PCOS women.

Table 4. Odds ratio (OR) of overweight, obesity, insulin resistance (IR), hypothyroidism, and hyperprolactinemia in PCOS women

| Variable | PCOS women (study group) | Non-PCOS controls | Odds ratio (95% CI); p-value |
|----------|--------------------------|-------------------|----------------------------|
| BMI 25-29.9 kg/m² | 51 (42.5) | 26 (21.7) | 2.67 (1.5-4.7); 0.0007* |
| BMI < 25 kg/m² | 69 (57.5) | 94 (78.3) | 3.4 (1.85-6.3); 0.0001* |
| BMI ≥ 30 kg/m² | 47 (39.17) | 19 (15.8) | 3.3 (1.87-5.9); 0.0001* |
| WC > 35 inches | 53 (44.17) | 23 (19.17) | 4.8 (2.6-8.8); 0.0001* |
| WC < 35 inches | 67 (55.13) | 97 (80.83) | 4.29 (1.9-9.4); 0.0003* |
| G/I ratio < 4.5 | 57 (47.5) | 19 (15.8) | 4.27 (2.1-8.5); 0.0001* |
| G/I ratio > 4.5 | 63 (52.5) | 101 (84.2) | 4.27 (2.1-8.5); 0.0001* |
| TSH ≥ 4.1 mIU/ml | 31 (25.8) | 9 (7.5) | 4.27 (2.1-8.5); 0.0001* |
| TSH < 4.1 mIU/ml | 89 (74.2) | 111 (92.5) | 4.27 (2.1-8.5); 0.0001* |
| Prolactin > 29 ng/ml (> 614 mIU/ml) | 41 (34.17) | 13 (10.8) | 4.27 (2.1-8.5); 0.0001* |
| Prolactin < 29 ng/ml (< 614 mIU/ml) | 79 (65.83) | 107 (89.2) | 4.27 (2.1-8.5); 0.0001* |

PCOS – polycystic ovary syndrome, WC – waist circumference, G/I – glucose/insulin, TSH – thyroid stimulating hormone, CI – confidence interval. * significant difference. Data presented as number and percentage (%).
ovarian hyperandrogenism (mainly testosterone and androstenedione), and increased PCOS severity [9].

Similarly, Lerchbaum et al. [20] and Abdelazim et al. [21] found the androstenedione, and testosterone are the main elevated ovarian androgens in PCOS.

This study found that the TSH, and prolactin were significantly high in studied PCOS women, and 47.5% of the studied PCOS women had IR. The PCOS women had significantly higher odds, and relative risks of IR, hypothyroidism, and hyperprolactinemia than controls.

The current study was the first study designed to determine, and explain the association between IR, hypothyroidism, hyperprolactinemia, and PCOS.

Women refused to give consent or to participate was the only limitation faced during this study. Larger future studies needed to confirm the association, and the prevalence of IR, hypothyroidism, and hyperprolactinemia among PCOS women.

Conclusions

TSH, and prolactin were significantly high in studied PCOS women, and 47.5% of the studied PCOS women had IR. The PCOS women had significantly higher odds, and relative risks of IR, hypothyroidism, and hyperprolactinemia than controls. IR, hypothyroidism, and hyperprolactinemia are common endocrine disorders associated with PCOS.

Disclosure

The authors report no conflict of interest.

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