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Brief communication (Original)

Hyperandrogenemia is associated with thin endometrium in reproductive-aged Thai women with polycystic ovary syndrome

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Background: Pelvic ultrasonography is necessary for the diagnosis of polycystic ovary syndrome (PCOS). Compared with transabdominal ultrasonography, a transvaginal approach provides better endometrial imaging, but is more invasive. A thick endometrium is associated with endometrial abnormalities indicating further surveillance.

Objectives: We determined factors associating with endometrial thickness in PCOS Thai women. The information is useful to identify patients who need endometrial surveillance.

Methods: One hundred sixty-nine Thai women with PCOS diagnosed using revised Rotterdam 2003 criteria were examined for weight, height, waist circumference, and signs of hyperandrogenism. Endometrial thickness was determined by ultrasonography. Venous blood samples were collected after 12-hour fasting period and at 2 hours after 75-gram oral glucose loading.

Results: Endometrial thickness had moderate correlation with BMI ($r = 0.207$, $p = 0.007$), 2-hour glucose ($r = 0.227$, $p = 0.003$), and serum total testosterone ($r = –0.278$, $p < 0.001$); it had weak to null correlation ($r < 0.2$) with age, duration of amenorrhea, waist circumference, Ferriman–Gallwey score, and other parameters of insulin resistance and hyperandrogenemia. Multiple logistic regression analysis demonstrated that important factors associating with endometrial thickness ≥7 mm were total testosterone >0.8 ng/mL (OR = 0.241, 95%CI 0.118–0.493, $p < 0.001$) and BMI ≥23.5 kg/m^2 (OR = 2.431, 95%CI.1.196–4.939, $p = 0.014$).

Conclusions: Endometrial thickness in PCOS Thai women has significantly inverse correlation with serum total testosterone and positive correlation with BMI. Endometrial thickness measurement using transvaginal ultrasonography may be unnecessary for PCOS Thai women with hyperandrogenism.

Keywords: Endometrial thickness, hyperandrogenemia, polycystic ovary syndrome, Thai

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in reproductive-aged women. The pathophysiology of this syndrome includes chronic anovulation, hyperandrogenemia, and insulin resistance leading to various clinical manifestations, which are abnormal uterine bleeding, hirsutism, and infertility. Prevalence of PCOS in reproductive-aged women varies from 4% to 7 % depending on the criteria for diagnosis [1]. The 2003 revised Rotterdam criteria is currently the most implemented tool worldwide[2]. To diagnose PCOS using these criteria, the necessary information includes clinical data (menstrual history and clinical manifestation of hyperandrogenism), a blood test (to show hyperandrogenemia and to rule out other endocrinopathies), and an ultrasonogram of the ovaries.

PCOS patients are prone to have endometrial abnormalities including endometrial polyps, endometrial hyperplasia, and endometrial cancer [1, 3, 4]. In particular, for endometrial cancer [1, 4, 6] the PCOS patients need preventive measures including endometrial surveillance to detect endometrial lesions, and/or progestogen supplementation to oppose the endometrial stimulating effect of estrogen. Currently, there is no standard guideline for endometrial surveillance in women with PCOS. Moreover, progestogen therapy has limitations for long-term

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compliance and side effects [7], it should be provided only to the women who need it, e.g. the women at high risk of endometrial neoplasia.

Measurement of endometrial thickness using ultrasonography is a promising tool for endometrial surveillance. It has benefit for determining endometrial cancer risk in women with postmenopausal bleeding [8]. Moreover, there is evidence that PCOS women with an endometrial thickness of ≥7 mm are at high risk of endometrial neoplasia [3]. Therefore, ultrasonography in PCOS is useful not only for the diagnosis of polycystic ovary (PCO), but also for the screening of abnormal endometrium. Ultrasonography for the evaluation of ovarian morphology can be performed using transabdominal or transvaginal ultrasonography, but the latter is superior to the former in detecting endometrial abnormalities [9]. However, transvaginal ultrasonography is deemed invasive for Thai women, especially for those who are young and virginal.

The present study aimed to identify factors associating with endometrial thickness in PCOS Thai women. The information would be useful for identifying a PCOS woman who needs endometrial surveillance. If the patient is reluctant to undergo transvaginal or transrectal ultrasonography, and has no need for endometrial surveillance, the diagnosis of PCO morphology can be obtained using transabdominal ultrasonography, which is less invasive than the transvaginal ultrasonography.

Materials and methods

A cross-sectional study was conducted in the Gynecologic Endocrinology Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, a tertiary-care university hospital. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the study protocol was approved by the Siriraj Institutional Review Board.

Participants

Participants were PCOS Thai women registering to the Siriraj PCOS project, which had been established at our clinic since 2007 [10]. A diagnosis of PCOS was made according to the inclusion and exclusion criteria of the revised Rotterdam 2003 criteria [2]. Additional exclusion criteria were women who had previous surgery of one or both ovaries, used hormonal treatment, took medication for dyslipidemia within 3 months, or took a steroid within 6 months before participation in the study. All participants were interviewed for demographic data. The detailed method of clinical examination was published in our previous report [10].

Venous blood samples were obtained twice from each patient. The first sample was drawn at 8:00–10:00 AM after a 12-hour fasting period and the second sample at 2 hours after 75-g oral glucose loading. The fasting sample was tested for glucose, lipid (cholesterol, triglyceride, high density lipoprotein cholesterol, and low density lipoprotein cholesterol), hormones (insulin, cortisol, thyroid stimulating hormone, prolactin, and androgens), and sex hormone binding globulin; whereas the 2-hour sample was tested for glucose and insulin. All blood samples were analyzed at the laboratory units of the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, an IS0 15189 certified laboratory. The techniques used for biochemical and hormonal assays were published in our previous report [10].

Ultrasonography was performed using an ultrasound machine (LOGIG 5 PRO, GE Medical System Asia Company) to evaluate ovarian morphology and endometrial thickness. The thickness of endometrium was measured at the widest part of endometrial echo of the uterine ultrasonogram in sagittal view. The measurement had intra-and interobserver variation <5%.

Definitions

Clinical hyperandrogenism was defined as a modified Ferriman–Gallwey score ≥8 [11]. Hyperandrogenemia was considered if a patient had at least one abnormal value of serum androgens, i.e. free testosterone >6 pg/mL, total testosterone >0.8 ng/dL, or dehydroepiandrosterone sulphate (DHEAS) >350 μg/dL [12]. Insulin resistance was considered if a patient had at least one abnormal value of the following carbohydrate metabolic profiles, i.e. fasting blood glucose ≥ 100 mg/dL, 2-hour glucose ≥140 [13], fasting glucose and insulin ratio <4.5 [14], or homeostatic measurement assessment-insulin resistance (HOMA-IR) >2 [15].

Statistical analysis

Sample size was calculated using a formula for descriptive data. When an estimated prevalence of endometrial thickness ≥7 mm (p) = 45% (from our pilot study), precision error of estimation (20% of p) =

0.09, and $\alpha = 0.05$, a sample size of at least 117 was needed. Statistical analysis was performed using the SPSS version 14.0. Data are presented as mean and standard deviation (SD), median and interquartile range (IQR), number (n) and percent (%), or odds ratio (OR) and 95% confidence interval (CI). Continuous data were tested for normality using a histogram, normal Q-Q plot, and Kolmogorov–Smirnov test. Spearman's rank-order correlation was used to determine the correlation coefficient (r) between endometrial thickness and continuous variables. Multiple logistic regression analysis was used to determine the significant factors associating with an endometrial thickness ≥7 mm. All tests were two-sided, and had a significance level at $p < 0.05$.

Results

Among 200 Thai women presenting with oligomenorrhea or amenorrhea, 169 were diagnosed to have PCOS and were included into the present study. None of them had undergone previous pelvic surgery or ever been pregnant.

Table 1 shows characteristics of the participants. The mean ± SD of age was 25.20 ± 5.75 y, body mass index was 25.79 ± 7.47 kg/m^2, and waist circumference was 81.81 ± 16.15 cm. Of all patients, 46 (27.22%) had morbid obesity (BMI ≥30 kg/m^2), 43 (25.44%) had acanthosis nigricans, and 18 (13.85%) had clinical hyperandrogenism, The prevalence of insulin resistance using fasting glucose/insulin ratio and the HOMA-IR cut-off were 20.71% and 46.15%, respectively. The prevalences of hyperandrogenemia using total testosterone, free testosterone, and DHEAS cut-off were 36.09%, 73.96%, and 15.38%, respectively.

Table 1. Characteristics of 169 Thai women with polycystic ovary syndrome (PCOS)

Characteristics	
Clinical	
Age (y)	25.20 ± 5.75
Duration since last menstrual period (mo)	4.43 [3–4]
Systolic BP ≥130 mmHg	19 (11.24)
Diastolic BP ≥85 mmHg	11 (6.51)
Body mass index (kg/m^2)	25.79 ± 7.47
≥23.5	90 (53.25)
≥30	46 (27.22)
Waist circumference (cm)	81.82 ± 16.15
≥80	81 (47.93)
>88	55 (32.54)
Presence of acanthosis nigricans	43 (25.44)
Modified Ferriman–Gallwey Score (n = 130)*	2 [0–8]
≥8	18 (13.85)
Endometrial thickness	6.90 [5.70–8.50]
Carbohydrate metabolic profiles	
Fasting blood glucose (mg/dL)	85.2 [77.0–87.0]
≥100	11 (6.51)
≥126	6 (3.55)
Fasting insulin (U/mL)	15.8 [5.7–18.2]
2-h blood glucose (mg/dL)	114.6 [82.0–128.5]
≥140	29 (17.16)
≥200	9 (5.32)
2-h insulin (U/mL)	103.7 [39.1–142.6]
≥100	63 (37.28)
≥300	5 (29.58)
Fasting glucose/insulin ratio	11.2 [5.0–13.9]
<4.5	35 (20.71)
HOMA-IR	3.5 [1.1–4.1]
≥2	78 (46.15)

Table 1. Characteristics of 169 Thai women with polycystic ovary syndrome (PCOS)

Characteristics	
Androgens	
Total testosterone (ng/mL)	0.7 [0.4–0.9]
>0.8	61 (36.09)
SHBG (nmol/L)	37.0 [21.0–55.5]
Free testosterone (ng/mL)	0.013 [0.006–0.017]
>0.006	125 (73.96)
Free testosterone Index	11.5 [3.33–11.11]
Bioavailable testosterone (ng/dL)	0.33 [0.14–0.41]
DHEAS (μg/dL)	252.4 [176.5–299.9]
>350	26 (15.38)

Data are mean standard deviation, median [interquartile range], or number (%). BP = blood pressure, HOMA-IR = homeostatic measurement assessment-insulin resistance, DHEAS = dehydroepiandrosterone sulphate, SHBG = sex hormone binding globulin

Table 2 shows variables associating with endometrial thickness in PCOS women. Spearman's rank correlation showed that endometrial thickness had moderate correlation (r >0.2, $p < 0.05$) with BMI ($r = 0.207$, $p = 0.007$), 2-hour glucose ($r = 0.227$, $p = 0.003$), and serum total testosterone ($r = –0.278$, $p < 0.001$); it had weak correlation ($r < 0.2$, $p < 0.05$) with fasting blood glucose ($r = 0.170$, $p = 0.027$), HOMA-IR ($r = 0.163$, $p = 0.035$), and sex hormone binding globulin ($r = 0.153$, $p = 0.047$); it had no correlation ($r < 0.2$, $p > 0.05$) with age, duration since LMP, waist circumference, modified Ferriman–Gallwey score, and other parameters of insulin resistance and hyperandrogenemia (r varying from –0.015 to 0.150).

Table 2. Factors associating with endometrial thickness in 169 PCOS Thai women

Factors	*r*	*p*
Age (y)	0.150	0.052
Duration since last menstrual period (mo)	–0.015	0.846
Body mass index (kg/m^2)	0.207	0.007
Waist circumference (cm)	0.148	0.055
Modified Ferriman–Gallwey score	–0.038	0.669
Carbohydrate metabolic profiles		
Fasting blood glucose (mg/dL)	0.170	0.027
Fasting insulin (μU/mL)	0.148	0.055
2-h blood glucose (mg/dL)	0.227	0.003
2-h insulin (μU/mL)	0.117	0.129
Fasting glucose/insulin ratio	–0.132	0.088
HOMA-IR	0.163	0.035
Androgens		
Total testosterone (ng/mL)	–0.278	<0.001
SHBG (nmol/L)	–0.153	0.047
Free testosterone (ng/mL)	–0.079	0.310
Free testosterone index	–0.015	0.845
Bioavailable testosterone	–0.099	0.203
DHEAS (μg/dL)	–0.069	0.370

Data were analyzed using Spearman's rank correlation. DHEAS = dehydroepiandrosterone sulphate, HOMA-IR = homeostatic measurement assessment-insulin resistance, SHBG = sex hormone binding globulin

Multiple logistic regression analysis was used to identify the significant factors associating with an endometrial thickness ≥7 mm. Factors included in the model were those that had moderate correlation with endometrial thickness, i.e. BMI (<23.5 vs. ≥23.5 kg/m^2), 2-h glucose (<140 vs. ≥140 mg/mL), and total testosterone (≤0.8 vs. >0.8 ng/mL). The important factors were total testosterone >0.8 ng/mL (OR = 0.241, 95%CI 0.118–0.493, $p < 0.001$) and BMI ≥23.5 kg/m^2 (OR = 2.431, 95%CI.1.196–4.939, $p = 0.014$).

Discussion

Ultrasonographic measurement of endometrial thickness is a valuable tool for management of postmenopausal bleeding. A meta-analysis indicated that women with postmenopausal bleeding and an endometrial thickness >5 mm had a 30% risk of endometrial cancer [8]. The histopathology of endometrial tissue is necessary for a definitive diagnosis in these women. The endometrial thickness in the reproductive-aged women represents less association with the cancer because both thickness and echoic pattern of endometrium undergo cyclical transformation in accordance with the cyclical rhythm of ovarian hormones. In the PCOS women, the absence of such a cyclical rhythm results in an unopposed estrogen environment consequently increases risks of endometrial hyperplasia and cancer. In 2001, Cheung demonstrated the value of endometrial thickness measurement in Canadian women with PCOS. They found that PCOS women with endometrial thickness ≥7 mm had 35.7% risk of endometrial neoplasia whereas none with a thickness of <7 mm had the risk [3].

In the present study, approximately 46% of PCOS women had endometrial thickness ≥7 mm. In concordance with the previous reports [3, 16], there was no association between endometrial thickness and duration since LMP. This supports the hypothesis that the uterine bleeding of PCOS women is estrogen breakthrough bleeding and the endometrium undergoes incomplete shedding during the bleeding [1].

Apart from chronic anovulation, PCOS women also have hyperinsulinemia, hyperandrogenemia, and central obesity; all of these have a complex interaction with metabolic derangement and hormonal disturbance. As a result, the endometrial differentiation becomes further impaired. Previous study demonstrated the positive correlation between endometrial thickness, insulin resistance, and central obesity [6]. Hyperinsulinemia affects endometrial proliferation by direct action of insulin like growth factor (IGF) on IGF receptor which locates on endometrial cell membranes [17]. Central obesity indirectly involves endometrial proliferation by promoting the peripheral conversion of androgens to estrogens. Androgens have dual effects on endometrial differentiation. Androgens directly inhibit endometrial growth via an unknown mechanism [18]. On the other hand, androgens, after conversion to estrogens, stimulate endometrial proliferation. Many studies demonstrated that hyperandrogenemia significantly increased endometrial cancer risk in pre- and post-menopausal women [19-22].

In the present study, we found that endometrial thickness had a significantly inverse correlation with total testosterone, and a positive correlation with BMI. The endometrial thickness had only weak to null association with age, duration since LMP, waist circumference, various parameters of insulin resistance, and other parameters of hyperandrogenism. This suggested that endometrial thickness in our population was affected more by hyperandrogenemia than by insulin resistance. Because our population was relatively thin, the ability to convert androgens to estrogens would be less than that of obese population. Hence, hyperandrogenemia in our population had inhibitory rather than stimulatory effect on endometrium.

From the aforementioned mechanism, PCOS women are at risk of endometrial neoplasia. However, there is as yet no standard guideline for endometrial surveillance in this population. Our finding that PCOS Thai women with hyperandrogenemia, as compared with those without, had relatively thin endometrium, suggesting that this specific group of women with PCOS might have lower risk of endometrial neoplasia.

The present study has some limitations. Firstly, we did not routinely perform endometrial sampling in our population, because the procedure is considered invasive and inappropriate for young women. Therefore, we could not confirm that women with PCOS with a thinner endometrium had lower risk of endometrial neoplasia than those with a thicker endometrium. To date, there is limited data regarding endometrial histopathology in PCOS women without abnormal uterine bleeding; more studies are needed to provide information regarding this issue. Secondly,

we did not measure estrogen and progesterone levels in our population. These two reproductive hormones are important factors affecting endometrial thickness and risk of endometrial neoplasia; therefore they might confound our result. However, the evaluation of these hormones is not necessary in clinical practice. Because all of our participants had PCO; they should not have low estrogen. Because none of them had eumenorrhea, corpus luteum, or a follicle >9 mm; they should not have ovulation around the time of evaluation for endometrial thickness. Although ovulation could sporadically occur in PCOS women with eumenorrhea [23], this was not present in our study population. This evidence indirectly indicated that our result should not be confounded by reproductive hormones.

In conclusion, endometrial thickness in Thai women with PCOS has a significantly inverse correlation with serum total testosterone and positive correlation with BMI. The thickness has weak to null association with age, duration of amenorrhea, various parameters of insulin resistance, and other parameters of hyperandrogenism.

Therefore endometrial thickness measurement using transvaginal ultrasonography might be unnecessary for Thai women with PCOS and hyperandrogenemia. If these patients are reluctant to undergo transvaginal ultrasonography, they can be examined using transabdominal ultrasonography to evaluate ovarian morphology alone.

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