The Percentages of Endometrial Hyperplasia and Endometrial Cancer among Polycystic Ovary Syndrome (PCOS) Patients Presenting with Abnormal Menstrual Pattern

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Objective: *Assess the occurrence of endometrial hyperplasia and endometrial cancer among PCOS patients having abnormal menstrual pattern. Endometrial thickness and other clinical characteristics associated with endometrial hyperplasia and endometrial cancer were also evaluated.*

Material and Method: *Women with PCOS and abnormal menstrual pattern were enrolled into this cross-sectional study. Endometrial thicknesses were evaluated using transvaginal sonography. Endometrial aspiration was performed with endometrial aspirator and sent for pathology.*

Results: *Out of 52 PCOS patients with abnormal menstrual pattern, nine (17.3%) and one (1.9%) had endometrial hyperplasia and endometrial cancer, respectively. There was no significant difference in mean endometrial thickness between those who had abnormal and normal endometrium (8.19±2.58 mm and 7.76±4.03 mm, respectively). However, BMI and age of patients with abnormal endometrium were significantly higher and older than those with normal endometrium (p = 0.031 and p = 0.009, respectively).*

Conclusion: *Nineteen point two percent (19.2%) of patients with PCOS and abnormal menstrual pattern had endometrial hyperplasia or endometrial cancer. Endometrial thickness was not different between those with abnormal and normal endometrium.*

Keywords: *Polycystic ovary syndrome (PCOS), Abnormal menstrual pattern, Endometrial hyperplasia, Endometrial carcinoma*

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder that affects 5 to 10% of women who are of reproductive age. The most common presentation of PCOS is abnormal menstruation such as oligomenorrhea, amenorrhea, or dysfunctional uterine bleeding. In 1949[1]. It was first reported that PCOS was associated with endometrial cancer and many subsequent studies support this finding[2-4]. When there is unopposed prolonged production of estrogen, it results in chronic anovulation that can progress into endometrial hyperplasia, which is a precursor for endometrial cancer[5-7]. Currently most PCOS patients presenting with abnormal menstruation are treated with hormonal treatment with no known endometrial pathology. Sonographic findings may reveal an obvious intracavitary lesion such as endometrial polyp, submucous myoma, or marked thickening of the endometrium. However, there is no consensus regarding the cut-off points for the endometrial thickness (ET) that can predict premalignant and malignant lesions of the endometrium. Some authors suggest that endometrial biopsy should be performed when ET is greater than 12 mm in premenopausal women with a history of prolonged anovulation because of an increased risk for developing endometrial hyperplasia or cancer[8]. The prevalence of endometrial hyperplasia with idiopathic anovulation and PCOS among Thai women with amenorrhea was 45% and 48%, respectively[9]. Nowadays, endometrial cancer is frequently found in younger women[10]. A study from Thailand reported that the prevalence of endometrial adenocarcinoma was 10% among obese or overweight (BMI >25 kg/m^2) women younger than 40 years old and unable to become pregnant[11].

The aim of the present research was to assess the percentages of endometrial hyperplasia and endometrial cancer among PCOS patients presenting

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with abnormal menstrual pattern. The second objective was to determine if the endometrial thickness detected by transvaginal ultrasound and other clinical factors could predict the development of endometrial hyperplasia or endometrial cancer among these patients.

Material and Method

The present study is a cross-sectional descriptive study that recruited women of reproductive age who were diagnosed with PCOS and had abnormal menstrual pattern, attending the outpatient clinics at the King Chulalongkorn Memorial Hospital between June 2012 and June 2013. The present study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University. Informed consent was obtained from each patient before enrollment into the study.

Study population

Fifty-two PCOS women with abnormal menstrual pattern were enrolled into the present study. The diagnosis of PCOS was based on the Rotterdam Criteria 2003[12]. In the present study, abnormal menstrual pattern included oligomenorrhea (menstrual interval of >35 days), polymenorrhea (menstrual interval of <24 days), menorrhagia (amount of menstrual blood >80 ml per one cycle and duration of period lasting for >7 days but have a regular menstrual interval), metrorrhagia (irregular menstrual interval), menometrorrhagia (amount of menstrual blood >80 ml and duration of period lasting for >7 days with irregular menstrual interval), hypermenorrhea (amount of menstrual blood >80 ml with regular menstrual interval and normal duration), hypomenorrhea (amount of menstrual blood <30 ml with regular menstrual interval and normal duration), and amenorrhea (no period for at least three consecutive months)[13].

Intervention

Physical examinations were performed, and menstrual history and abnormal menstrual pattern were collected from interviewing the patients. Transvaginal ultrasound (TVS) was done by the first author of this study (NP) using 8 MHz transvaginal probe (LOGIQ™ P5, GE Healthcare, USA). Endometrium aligning the uterus along the central longitudinal axis was identified and the thickness was measured from the echogenic interface between the endometrium and myometrium to the opposite interface at the point of maximum thickness. Endometrium thickness (ET) was measured three times and the average value was used for analysis. After transvaginal sonography, endometrial biopsy was carried out by using an endometrial aspirator (Endocell®, The Wallach Endocell, USA). The tissue was then sent for pathology. The criteria for abnormal endometrial pathology were according to WHO's 2003 Classification for the tumor of the breast and female genital organs[14]. The pathological results were divided into two groups: normal and abnormal pathologies including endometrial hyperplasia and endometrial cancer.

Statistical analysis

Statistical analysis was performed using SPSS Software Version 16 (SPSS, Inc., Chicago, IL, USA). The demographic data was compared by mean ± SD. Unpaired t-test or Mann-Whitney U test was used to compare the variables between patients with normal endometrial pathology and abnormal endometrial pathology, when appropriate. The binary logistic regression analysis was used to determine the clinical risk factors for endometrial hyperplasia and endometrial cancer. A p-value of <0.05 was considered as statistically significant for all analysis.

Results

Demographic data

Fifty-two PCOS patients were classified according to the endometrial pathology and divided into two groups: abnormal endometrial pathology group (n = 10) and the normal endometrial pathology group (n = 42). Abnormal endometrial pathologies were defined as simple hyperplasia with or without atypia, complex hyperplasia with or without atypia and endometrial carcinoma. Normal endometrial pathologies were defined as proliferative endometrium and secretory endometrium. Among 10 patients with abnormal endometrial pathology, seven had simple hyperplasia without atypia, one had simple hyperplasia with atypia, another one had complex hyperplasia without atypia, and the other had a well-differentiated endometrioid adenocarcinoma. The demographic data for all patients are shown in Table 1.

The mean ET in the abnormal endometrial group and normal endometrial group were no significant difference, comparable at 8.19±2.50 mm and 7.76±4.04 mm ($p = 0.27$) respectively. However, BMI and age in patients from the abnormal endometrial group were significantly higher and older than the patients from the normal endometrial group ($p = 0.01$ and $p = 0.03$, respectively).

Table 1. Demographic data

Patient data	All participants (n = 52)	Abnormal endometrial group (n = 10)	Normal endometrial group (n = 42)	p-value
Age (year)	32.37±6.10	37.70±8.20	30.98±4.80	0.03
Age of menarche (year)	13.65±1.68	13.20±2.10	13.88±1.56	0.36
BMI (kg/m^2)	26.12±7.04	31.27±6.50	24.89±6.65	0.01
Duration of disease (year)	8.29±5.69	9.10±80.0	8.09±5.09	0.71
ET (millimeter)	7.84±3.77	8.19±2.50	7.76±4.04	0.68

Data are presented as mean ± SD
BMI = body mass index; ET = endometrial thickness

Table 2. Clinical parameters associated with the risk for developing abnormal endometrial pathology based on the binary logistic regression analysis

Clinical parameters	Crude OR*	95% CI**
Age (year)	1.19	1.05-1.35
BMI (kg/m^2)	1.13	1.02-1.26
Menarche (year)	0.78	0.50-1.20
Duration of disease (year)	1.03	0.92-1.16
ET (millimeter)	1.03	0.86-1.23

* Crude OR: unadjusted odds ratios
** 95% CI: 95% confidence interval
BMI = body mass index; ET = endometrial thickness

From the logistic regression analysis (Table 2), BMI and age were the two clinical parameters that were found to be associated with abnormal endometrial pathologies (unadjusted odd ratio (OR) 1.13; 95% confidence interval (CI) 1.02-1.25 and OR 1.19; 95% CI 1.05-1.35, respectively).

The percentages for abnormal endometrial pathology in the present study (Table 3) were 17.3% for endometrial hyperplasia and 1.9% for endometrial carcinoma. In the abnormal endometrial pathology group, 60% of the patients (n = 6) had oligomenorrhea whereas 40% (n = 4) had menometrorrhagia.

The total prevalence for endometrial polyps (Table 4) was 47.6% of which 38.5% were from the abnormal endometrial group and 34.6% were from the normal endometrial group; the prevalence for endometrial polyps was comparable across both groups.

Discussion

The purpose of the present study was to determine the percentages of endometrial hyperplasia and endometrial cancer among PCOS patients presenting with abnormal menstrual patterns. Since chronic anovulation in PCOS patients is associated with prolonged, unopposed estrogen stimulation of the endometrium, therefore this can result in an increased risk for developing endometrial hyperplasia and endometrial cancer. Nowadays PCOS patients presenting with abnormal menstrual pattern are usually treated with hormonal therapy with no known endometrial pathology. For this reason, the present study also assessed whether there were any clinical parameters such as endometrial thickness detected by ultrasound that can predict endometrial hyperplasia and endometrial cancer among these patients.

The percentage of endometrial hyperplasia in the present study was 17.3%, which is much lower when compared to the other studies. According to the study of Yada et al the prevalence of endometrial hyperplasia in anovulatory women was 45.6%[9]. The prevalence of endometrial hyperplasia from other studies was 35.7% among PCOS patients presenting with an infertility problem[15] and 20% among premenopausal women presenting with abnormal menstrual bleeding[16]. This discrepancy may be due to the different population studied. It is possible that PCOS patients with amenorrhea will have a higher prevalence of endometrial hyperplasia than PCOS patients with abnormal menstrual pattern.

On the other hand, the percentage of endometrial carcinoma was similar to those reported previously. In our study, the percentage of endometrial carcinoma was 1.9% whereas in Korea, the percentage was 1.7%[17]. Likewise, the cell type detected in the present study, well-differentiated endometrioid adenocarcinoma, was also detected in the Korean study[17]. Furthermore, the patient in the present study who had well differentiated endometrioid adenocarcinoma was only 26-year-old and her BMI was 42.19 kg/m^2. Her clinical presentation was oligomenorrhea for six months.

Table 3. Comparison of the menstrual patterns between the normal and abnormal endometrial group

Pattern of menstruation	Abnormal endometrial group (n = 10)	Normal endometrial group (n = 42)	p-value
Oligomenorrhea	6 (60%)	31 (78.80%)	0.41
Menometrorrhagia	4 (40%)	9 (21.40%)	0.36
Amenorrhea	-	2 (4.20%)	0.64

Table 4. Prevalence of endometrial polyp

Endometrial pathology	Endometrial polyp	No endometrial polyp	Total
Normal endometrial group	18 (34.60%)	24 (46.20%)	42 (80.80%)
Abnormal endometrial group	2 (38.50%)	8 (15.40%)	10 (19.20%)

As for the menstrual pattern of the present study, the abnormal menstrual pattern was similar between the normal and abnormal endometrial groups. This result is quite different from that of Cheung et al[15], which reported that intermenstrual interval of more than three months was associated with endometrial hyperplasia.

With regards to the clinical parameters associated with endometrial hyperplasia and endometrial cancer. BMI and the age of the patients from the abnormal endometrial group were found to be significantly higher and older than in the normal endometrial group. These results are consistent with those studies conducted in peri- and post-menopausal women which showed that older age and obesity were associated with endometrial hyperplasia[15,17]. However, these results are different to a study conducted in Thai anovulatory women presenting with amenorrhea showing that there were no association between age and obesity for endometrial hyperplasia[9].

Another clinical parameter investigated in the present study was ET via ultrasound. There were no significant differences in ET between the abnormal endometrial and normal endometrial groups. These results are inconsistent with those conducted in infertile women with PCOS, which found that ET greater than 7 mm was associated with endometrial hyperplasia[15].

In the present study, the percentages of endometrial polyps were 38.5% and 34.6% for the abnormal endometrial group and normal endometrial group respectively. However, it has been reported that the prevalence of pre-malignant or malignancy arising in endometrial polyps was increased among PCOS women or patients with multiple polyps (OR 9.6; 95% CI 2.5-37 and OR 31.3; 95% CI 3.9-254, respectively).

The pathophysiology to explain this result is still unclear but there is some evidence to suggest that endometrial polyps may be associated with unopposed estrogen[18]. Therefore, additional study is needed to assess the association between PCOS and endometrial polyps.

Limitations

Some of the limitations of the present study need to be considered. First, the present study is based on a small sample size and therefore it is possible that there was not enough power to detect certain clinical parameters to be associated endometrial hyperplasia and/or endometrial cancer. Future study with a larger sample size may be able to detect these associations. Second, the menstrual history including age of menarche and duration of abnormal menstrual pattern was collected by interviewing the patients, which may not be accurate due to the patients' recalled memories.

Conclusion

Percentage of abnormal endometrial pathology was 19.2% (17.3% for endometrial hyperplasia and 1.9% for endometrial cancer). Endometrial thickness detected by ultrasound cannot predict abnormal endometrial pathology in PCOS patients. BMI and age are clinical factors associated with endometrial hyperplasia and endometrial cancer. Therefore, the authors recommend endometrial biopsy to detect abnormal endometrial pathologies in obese PCOS patients presenting with abnormal menstrual pattern regardless of the endometrial thickness.

What is already known on this topic?

The association between PCOS and endometrial cancer is well established. This is caused by prolonged unopposed estrogen due to chronic anovulation that can progress into endometrial hyperplasia and endometrial cancer. Nowadays, there is no consensus regarding the cut-off points of ET for

prediction risk of endometrial hyperplasia or cancer in premenopausal or PCOS women. Some studies suggested that ET more than 12 mm in premenopausal women with prolonged anovulation might increase risk for abnormal endometrial pathology. A study in infertile PCOS women reported that the ET more than 7 mm was associated with endometrial hyperplasia.

A previous study in anovulatory Thai women demonstrated that the prevalence of endometrial hyperplasia was 45.6% but the present study included only anovulatory women presenting with amenorrhea.

What this study adds?

The percentage of abnormal endometrial pathology in PCOS patients presenting with abnormal menstrual pattern was 19.2% (17.3% for endometrial hyperplasia and 1.9% for endometrial cancer). There is no difference in endometrial thickness detected by transvaginal ultrasound between women with normal and abnormal endometrial pathology. The percentages of endometrial polyps in the present study were 38.5% and 34.6% in abnormal and normal endometrial group, respectively. The association between PCOS and endometrial polyps is needed to be investigated in future study.

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Potential conflicts of interest

None.

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ร้อยละของการเกิดเยื่อบุโพรงมดลูกหนาตัวผิดปกติและการเกิดมะเร็งเยื่อบุโพรงมดลูกในผู้ป่วยกลุ่มอาการที่รังไข่มีถุงน้ำหลายใบที่มีลักษณะประจำเดือนมาผิดปกติ

นภปกรณ์ ปราการสมุทร, พรทิพย์ สิรยาภิวัฒน์, สุรางค์ ตรีรัตนชาติ

วัตถุประสงค์: *วัตถุประสงค์หลักเพื่อศึกษาถึงร้อยละของการเกิดเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และการเกิดมะเร็งเยื่อบุโพรงมดลูกในผู้ป่วยกลุ่มอาการที่รังไข่มีถุงน้ำหลายใบที่มีลักษณะประจำเดือนมาผิดปกติหรือขาดประจำเดือน โดยมีวัตถุประสงค์รองเพื่อศึกษาลักษณะและความหนาของเยื่อบุโพรงมดลูกที่ได้จากการตรวจคลื่นเสียงความถี่สูงทางช่องคลอด รวมทั้งปัจจัยทางคลินิกที่สัมพันธ์กับการเกิดเยื่อบุโพรงมดลูกหนาตัวผิดปกติหรือมะเร็งเยื่อบุโพรงมดลูกในผู้ป่วยกลุ่มดังกล่าว*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาเชิงพรรณนาแบบตัดขวาง (cross-sectional study) ศึกษาในผู้ป่วยหญิงวัยเจริญพันธุ์ที่มีกลุ่มอาการที่รังไข่มีถุงน้ำหลายใบและมีลักษณะประจำเดือนมาผิดปกติหรือขาดประจำเดือน ที่มาตรวจที่โรงพยาบาลจุฬาลงกรณ์ตั้งแต่เดือนมิถุนายน พ.ศ. 2555 ถึง เดือนมิถุนายน พ.ศ. 2556 โดยผู้ป่วยกลุ่มดังกล่าวจะได้รับการตรวจคลื่นเสียงความถี่สูงทางช่องคลอดเพื่อวัดความหนาของเยื่อบุโพรงมดลูก และตรวจดูลักษณะของเยื่อบุโพรงมดลูก หลังจากนั้นจะเก็บเยื่อบุโพรงมดลูกด้วยอุปกรณ์ดูดเก็บเยื่อบุโพรงมดลูก เพื่อส่งตรวจทางพยาธิวิทยาต่อไป การศึกษานี้ได้แบ่งผู้ป่วยออกเป็นสองกลุ่มตามผลทางพยาธิวิทยาของเยื่อบุโพรงมดลูกคือ กลุ่มที่มีผลทางพยาธิวิทยาเป็นปกติและกลุ่มที่มีผลทางพยาธิวิทยาผิดปกติ ซึ่งประกอบด้วยลักษณะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก*

ผลการศึกษา: *การศึกษานี้มีผู้ป่วยเข้าร่วมทั้งหมด 52 ราย ร้อยละของโรคเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูกเท่ากับ 17.3 และ 1.9 ตามลำดับ เมื่อทำการเปรียบเทียบลักษณะทางคลินิกพบว่าความหนาของเยื่อบุโพรงมดลูกที่วัดจากคลื่นเสียงความถี่สูงทางช่องคลอดในผู้ป่วยทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (8.19±2.50 และ 7.76±4.03 มิลลิเมตร ตามลำดับ) แต่อย่างไรก็ดีในการศึกษานี้พบว่าดรรชนีมวลกายและอายุของผู้ป่วยกลุ่มที่มีผลทางพยาธิวิทยาผิดปกติ มีค่าสูงกว่าผู้ป่วยกลุ่มที่มีผลทางพยาธิวิทยาปกติอย่างมีนัยสำคัญทางสถิติ ($p = 0.03$ และ $p = 0.01$ ตามลำดับ)*

สรุป: *ร้อยละ 19.2 ของผู้ป่วยหญิงวัยเจริญพันธุ์ ที่มีกลุ่มอาการที่รังไข่มีถุงน้ำหลายใบและมีลักษณะประจำเดือนมาผิดปกติหรือขาดประจำเดือน พบมีพยาธิสภาพของเยื่อบุโพรงมดลูก ความหนาของเยื่อบุโพรงมดลูกที่วัดจากคลื่นเสียงความถี่สูงทางช่องคลอดไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ระหว่างกลุ่มที่ผลทางพยาธิวิทยาผิดปกติและปกติ*