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Polycystic ovary syndrome: early diagnosis and intervention are necessary for fertility preservation in young women with endometrial cancer under 35 years of age

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Abstract

Aim: Polycystic ovary syndrome (PCOS) is a significant risk factor for premenopausal endometrial cancer (EC) and/or atypical endometrial hyperplasia (AEH). The aim was to elucidate the clinical background and detailed menstrual history of EC and/or AEH in young women with PCOS.

Methods: From January 2001 to December 2013, women under 35 years of age who had been diagnosed with EC and/or AEH and who had been treated at Kumamoto University Hospital, Japan, were recruited. The patients' clinical characteristics, clinical stages of EC and/or AEH, medication and operation methods, endocrine profiles, and menstrual history were assessed retrospectively.

Results: Of all the cases of EC and/or AEH, 25 (4.6%) were under 35 years of age. The mean age was 29.0 years and all the patients were nulligravida. The clinical stages of EC and/or AEH that were identified included: AEH (five cases), stage IA (18 cases), IB (one case), and IIIA (one case). Fourteen (56%) cases met the criteria for PCOS. Both the Body Mass Index and Homeostatic Model Assessment–insulin resistance were significantly higher in the patients with PCOS than in the patients without PCOS. Medroxyprogesterone acetate therapy was not effective for the patients with PCOS and they underwent a hysterectomy more often than the patients without PCOS. All the patients with PCOS exhibited irregular menstruation or amenorrhea, the mean duration of which was 13.1 years before PCOS and EC and/or AEH were diagnosed.

Conclusion: Although both the patients with and without PCOS had irregular menstruation, the patients with PCOS were less likely to have fertility-sparing surgery than the patients without PCOS because they had more advanced disease or failed to respond to medroxyprogesterone acetate therapy.

KEYWORDS

atypical endometrial hyperplasia, endometrial cancer, insulin resistance, organ-sparing treatments, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 5%-8% of women of reproductive age.[1] This condition is characterized by a classical triad of hyperandrogenism, menstrual abnormalities, and polycystic ovaries.[2,3] Women with PCOS often exhibit the characteristics of metabolic syndrome and insulin resistance.[4]

Patients with PCOS are at risk for premenopausal endometrial cancer (EC) and/or atypical endometrial hyperplasia (AEH). Endometrial cancer is the fourth-most common malignancy in women and the most common gynecological cancer in the US.[5] Approximately 25% of women with EC are premenopausal and 5% of all cases are diagnosed at under 40 years of age.[6] The important risk factors for EC and/or AEH often present in patients with PCOS, including obesity, nulliparity, infertility, hypertension, diabetes, chronic anovulation, and unopposed estrogen supplementation.[7] The mechanism by which EC and/or AEH develops in patients with PCOS involves not only chronic anovulation but also insulin resistance.[8] Patients with PCOS therefore could be at increased risk of developing EC and/or AEH, particularly when endometrial shedding is infrequent or absent due to ovulation irregularities.[7,9] A recent meta-analysis has shown that patients with PCOS are approximately threefold more likely to develop EC,[10,11] but EC and/or AEH could be prevented in such patients if a diagnosis of PCOS is made early and appropriate interventions, including cyclic progestin therapy, are initiated in a timely manner. Therefore, the current study aimed to elucidate the risk of developing EC and/or AEH in patients with PCOS who are under 35 years of age and to identify preventive measures for this group.

2 | MATERIALS AND METHODS

Between January 2001 and December 2013, hospital records were used to identify a cohort of patients who were under 35 years of age, who had been diagnosed with EC and/or AEH, and who had been treated at Kumamoto University Hospital, Japan. A retrospective observational study was conducted. The clinical characteristics, pathological diagnosis of EC and/or AEH, conservative treatment or hysterectomy, endocrine profiles, and menstrual history were assessed retrospectively from the medical records.

The study's participants were divided into two groups, a PCOS group and a non-PCOS group, and PCOS was diagnosed by using the revised criteria that were proposed by the Japanese Society of Obstetrics and Gynecology (JSOG) in 2007.[12,13] The patients who had been treated prior to the criteria undergoing this revision were re-examined and the diagnosis of PCOS was reconfirmed. The clinical characteristics included the participants' age, parity, height, weight, menstruation regularity, and clinical stage of EC and/or AEH. The endocrine profiles included the plasma glucose, insulin, luteinizing hormone (LH), follicle-stimulating hormone, free testosterone, and prolactin (PRL) levels. The effect of medroxyprogesterone acetate (MPA) therapy (600 mg/d) and operation methods was assessed in the PCOS and non-PCOS groups. "Irregular" menstruation was defined as shorter than 24 days or longer than 39 days. A statistical analysis was carried out by using the Student's *t*-test or χ^2-test where appropriate and $P<.05$ was taken as the threshold level of significance.

3 | RESULTS

From January 2001 to December 2013, 539 cases of EC and/or AEH were treated in Kumamoto University Hospital, of which 25 (4.6%) were under 35 years of age. Table 1 provides their clinical characteristics. There were 14 (56%) cases that met the diagnostic criteria for PCOS, as revised by JSOG in 2007.[12,13] The mean age was 29.0 years (median: 30; range: 22-34) and all the patients were nulligravida. The mean age at menarche was not statistically different between the PCOS group and the non-PCOS group. The body mass index (BMI) was significantly higher in the PCOS group (33.9±9.1 vs 25.0±8.4 kg/m^2, $P=.019$). Twenty-two (88%) cases had irregular menstrual cycles (Table 1).

The Homeostatic Model Assessment–insulin resistance (HOMA-IR) was also significantly higher in the patients with PCOS (6.5±4.6 vs 2.4±2.8, $P=.033$) (Table 2), as were the levels of LH. The free serum testosterone tended to be higher in the PCOS group (1.39±0.7 vs 1.11±0.3 pg/mL, $P=.336$) (Table 2). The PRL tended to be higher in the non-PCOS group (18.4±15.2 vs 41.9±58.6 ng/mL, $P=.222$) (Table 2).

The clinical stages of EC and/or AEH were identified as follows: AEH (five cases), stage IA (18 cases), IB (one case), and IIIA (one case) (Table 3). The five cases that were identified with AEH were all patients without PCOS. The number of patients who had undergone conservative therapy with MPA was six (43%) and nine (82%) in the PCOS group and the non-PCOS group, respectively. In the PCOS group, MPA therapy was effective in two out of six (33%) cases, but eight out of nine (89%) cases in the non-PCOS group ($P<.05$) (Table 4). All the patients with stage IB and above underwent a hysterectomy. There were 13 and five cases of stage IA in the PCOS group and non-PCOS group, respectively. When limited to stage IA, dilatation and curettage as a fertility-sparing treatment was performed in only two out of 13 cases in the PCOS group, whereas four out of five patients in the non-PCOS group underwent this procedure. When the operation method was compared between the two groups, it was clear that the non-PCOS group participants were more likely to preserve their fecundity than the PCOS group participants ($P=.0007$) (Table 5).

TABLE 1 Clinical characteristics of the study's participants

Characteristic	PCOS group (n=14)	Non-PCOS group (n=11)
Age (years)	29.4±3.3 (22-33)	28.8±3.2 (24-34)
Menarche (years)	11.9±1.6 (10-14)	12.6±1.3 (11-15)
Body mass index (kg/m^2)	33.9±9.1 (19.1-50.4)[a]	25.0±8.4 (15.8-38.9)[a]
No. of irregular menstruation cycles	14 (100%)	8 (73%)

[a]$P<.03$.

TABLE 2 Endocrine profiles of the study's participants

Endocrine profile	PCOS group (n=14)	Non-PCOS group (n=11)
HOMA-IR	7.1±4.0 (2.39-15.00)[a]	2.4±2.8 (0.60-9.69)[a]
LH (mIU/mL)	9.0±5.3 (3.70-21.30)[b]	5.4±2.9 (2.10-11.20)[b]
LH/FSH	4.6±3.3 (1.25-13.40)	2.5±4.2 (0.40-13.18)
Free testosterone (pg/mL)	1.4±0.7 (0.60-2.70)	1.1±0.3 (0.80-1.40)
Prolactin (ng/mL)	18.4±15.2 (4.00-51.50)	34.7±29.9 (3.90-95.90)
No. of hyperprolactinemia episodes (>15 ng/mL)	6/12	9/11

[a]$P<.01$; [b]$P<.05$; FSH, follicle-stimulating hormone; HOMA–IR, Homeostatic Model Assessment–insulin resistance; LH, luteinizing hormone.

TABLE 3 Clinical stages of endometrial cancer and atypical endometrial hyperplasia (AEH)

Clinical stage	PCOS group (n=14)	Non-PCOS group (n=11)
AEH	0	5
IA	13	5
IB	1	0
IIIA	0	1

TABLE 4 Effect of medroxyprogesterone acetate therapy for endometrial cancer and atypical endometrial hyperplasia

Medroxyprogesterone acetate therapy	PCOS group (n=6)[a]	Non-PCOS group (n=9)[a]
Effective	2	8
Not effective	4	1

[a]$P<.05$.

TABLE 5 Surgical procedures for endometrial cancer and atypical endometrial hyperplasia

Surgical procedure	PCOS group (n=14)[a]	Non-PCOS group (n=11)[a]
Dilatation and curettage	2	9
Hysterectomy	12	2

[a]$P<.001$.

Among the 25 participants, 22 (88%) exhibited a history of oligomenorrhea or amenorrhea. At the time of the EC and/or AEH diagnosis, all 14 patients with PCOS had oligomenorrhea or amenorrhea, whereas eight out of 11 of the patients without PCOS had oligomenorrhea or amenorrhea. In the PCOS group, 11 out of 14 cases had irregular menstruation or amenorrhea during their adolescent period. The mean duration of oligomenorrhea or amenorrhea was 13.1 years (median: 16; range: 1-21) and 10.1 years (median: 10; range: 0-21) before been diagnosed with EC and/or AEH in the PCOS group and the non-PCOS group, respectively ($P=.335$) (Fig. 1).

4 | DISCUSSION

Patients with PCOS exhibit features of hyperandrogenism, chronic anovulation, and infertility.[14] Patients with PCOS often have obesity and insulin resistance, which are risk factors for EC and/or AEH. Among the total number of patients with EC and/or AEH studied herein, 56% (14 out of 25) were diagnosed with PCOS according to the criteria that were proposed by JSOG. As PCOS is diagnosed in <10% of women of reproductive age,[1] the prevalence of PCOS is relatively high in patients with EC and/or AEH. There were significant differences in the BMI and HOMA-IR between the patients with PCOS and the patients without PCOS. This is consistent with the fact that obesity and insulin resistance are associated with PCOS.[9]

The serum PRL, however, was non-significantly higher in the non-PCOS group than in the PCOS group. As elevated serum PRL levels are one of the major causes of irregular menstruation and as PRL might be important in the development of early neoplastic transformation, such as endometrial hyperplasia,[15] it follows that hyperprolactinemia might be an independent risk factor for premenopausal EC and/or AEH in the study's non-PCOS group.

When comparing the characteristics of EC and/or AEH by clinical stages and MPA therapy or surgical treatment between the PCOS group and the non-PCOS group, it was apparent that the PCOS group did not have AEH and that the patients in this group were less likely to have MPA therapy and fertility-sparing surgery, even in the same-stage IA. This result supports the idea that obesity and insulin resistance are independent risk factors for premenopausal EC and/or AEH.[16]

Chronic anovulation is one of the major risk factors for premenopausal EC and/or AEH. In the present study, 88% (22 out of 25) of the patients had irregular menstrual cycles that were suggestive of chronic anovulation. Although both the number of irregular menstruation cycles and the mean duration of oligomenorrhea or amenorrhea were not significantly different between the PCOS and non-PCOS groups, the PCOS group tended to have longer irregular menstruation or amenorrhea in their adolescent period. Therefore, this might be the reason for the PCOS group to be less likely to have fertility-sparing surgery. However, the diagnosis of PCOS in adolescents is difficult because the features of early normal pubertal development and PCOS are often similar.[17] Ultrasonography is less practical for the diagnosis of polycystic ovaries in adolescent girls, as the ovarian appearance and volume can vary during adolescence and the trans-vaginal modality is less preferred than the trans-abdominal approach.[18] Although irregular menstrual cycles in the 5 years after menarche are physiological

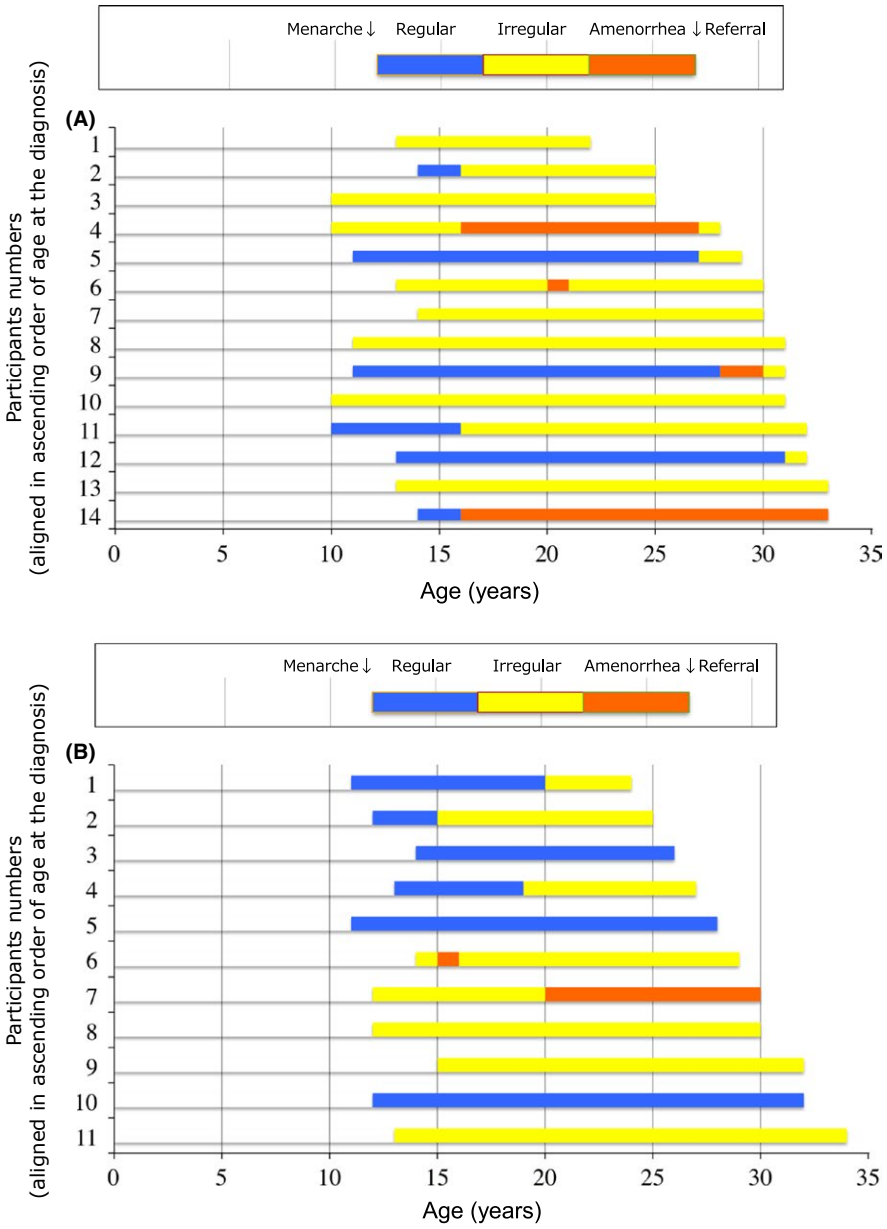

FIGURE 1 Menstrual history of the patients at the time of diagnosis. The participants were aligned in ascending order of age at the diagnosis of endometrial cancer and/or atypical endometrial hyperplasia. A, The patients with polycystic ovary syndrome and B, The patients without polycystic ovary syndrome

and no further clinical or endocrinological evaluation is suggested,[19] oligomenorrhea at age 18 years is better predicted by the pattern of menstrual cycles at the age of 15 years.[20] The diagnosis of PCOS is more difficult in the Asian population because hyperandrogenism is not as apparent as in the Caucasian population. Consequently, taking a menstrual history is likely to be the most powerful clue with which to diagnose PCOS. It has been suggested that anovulatory adolescents, even those who do not meet the criteria for a diagnosis of PCOS, should be followed up carefully and might be diagnosed at a later time.[21]

In conclusion, PCOS is frequently found among patients with EC and/or AEH who are under 35 years of age. These patients are more often obese, insulin-resistant, and less likely to have undergone fertility-sparing surgery than are patients without PCOS because they had more advanced disease or failed to respond to MPA therapy. Patients with PCOS exhibit a year-long duration of oligomenorrhea or amenorrhea prior to the diagnosis of PCOS. Therefore, early diagnosis and appropriate treatment are vital in the prevention of EC and/or AEH and in fertility preservation in patients with PCOS who are under 35 years of age.

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DISCLOSURE

Conflict of interest: The authors declare no conflict of interest. *Human and animal rights*: This article does not contain any study with human or animal participants that was performed by any of the authors.

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