Clinical presentation, hormonal profiles in nulliparous Korean women with polycystic ovarian morphology

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Summary

Purpose: The aim of this study was to determine the relationship between polycystic ovarian morphology (PCOM), ovarian morphology, anti-Müllerian hormone (AMH), and testosterone levels in young nulliparous Korean women. Materials and Methods: A total of 139 PCOM patients were evaluated from 2013 to 2018. The relationships between serum AMH levels and androgenic hormones, clinical signs of polycystic ovarian syndrome (PCOS), and ovarian morphology were investigated. Results: Irregular menstruation was the most common symptom in women with PCOM. This study found that hyperandrogenism was present in 26.6% of nulliparous Korean women with PCOM. The present findings support the use of serum AMH as a useful marker to reflect PCOM in cases where accurate ultrasounds are not available. Conclusions: This study found that PCOM did not equate with PCOS, although PCOM is one of the diagnostic criteria for PCOS. AMH levels were positively correlated with ovarian volume and AMH levels were not reflected by hyperandrogenism. Content: The use of serum AMH as a useful marker to reflect PCOM in cases where accurate ultrasounds are not available.

Key words: Polycystic ovaries; Ovarian volume; Follicle count; Follicle size; Endometrial thickness.

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of childbearing age and the leading cause of hyperandrogenism and oligoamenorrhea, which often results in infertility [1-3]. This is particularly the case for polycystic ovarian morphology (PCOM), which was initially defined as follicle number per ovary (FNPO) ≥ 12 and/or ovarian volume ≥ 10 mL [4, 5] in one cross-section of the ovary using ultrasonography. These different ovarian volume threshold values might depend on the variable clinical and metabolic characteristics of the populations studied. Ovarian size also varies with age, reaching a maximum during adolescence (1.3-3.8 years post-menarche), slowly decreasing during adulthood, and rapidly shrinking after menopause [2].

Three-dimensional ultrasound has been shown to be an objective tool for quantifying ovarian volume. The mean ovarian volume has been reported to vary between 10.6 and 16.7 mL in women with polycystic ovaries and from 5.2 to 8.7 mL in healthy women of reproductive age [6, 7]. With the advent of ultrasonography, follicular excess has become the main aspect of PCOM. Currently, there is an almost universal consensus on the choice of follicular excess and ovarian enlargement as criteria to define PCOM by ultrasound [2] but the clinical meaning of PCOM was not definitely known to be associated with PCOS.

The presence of PCOM may be regarded as a sign of hyperandrogenism and the same might apply for elevated serum AMH concentrations [8]. Follicular excess and high serum AMH levels are also linked to PCOS. PCOM or high serum AMH levels can be used as a substitute for either oligo- or anovulation or hyperandrogenism in diagnosing PCOS, provided other specific disorders have been excluded [8].

Only a few studies have investigated the relationship between serum AMH and the clinical signs of hyperandrogenism and menstrual regularity in women with PCOM. In this study, the authors sought to determine whether AMH levels were a useful biomarker for ovarian ultrasound characteristics in young women with PCOM by correlating serum AMH levels with follicular numbers, distribution, ovarian volume, and hyperandrogenism.

Materials and Methods

This cross-sectional study was conducted from January 2013 to January 2018 and the subjects were recruited from a single university hospital. After approval by the Institutional Ethics Committee (HCI3TISI0045), the study enrolled young nulliparous Korean women with PCOM combined with irregular menstrual cycles.

The exclusion criteria included pregnancy history, ovarian or androgen-secreting tumors, thyroid dysfunction, hyperprolactinemia, and previous ovarian surgical operations. No subject was taking insulin sensitizers or any medication (including oral contraceptives) known to influence the menstrual cycle. Amenorrhea was defined as the cessation of periods for more than three months. Oligomenorrhea was defined as less than six cycles per year and irregular menstruation was defined as menstrual cycle frequency less than
Table 1. — Epidemiologic Characteristics of PCOM Woman

| Characteristic                  | Mean ± SD | N (%)       |
|---------------------------------|-----------|-------------|
| Age (years)                     | 21.46 ± 3.64 | 360         |
| Height (cm)                     | 161.16 ± 5.97 | 360         |
| Weight (kg)                     | 60.27 ± 14.27 | 360         |
| BMI (kg/m²)                     | 23.19 ± 5.11  | 360         |
| Birth weight (kg)               | 3.18 ± 0.46   | 360         |
| Age of menarche (years)         | 13.76 ± 1.64  | 360         |
| Menstrual interval              |            |             |
| irregular                       | 128 (94.81%)  | 360         |
| regular                         | 7 (5.19%)     | 360         |
| Duration of menstruation (days) | 6.36 ± 2.26   | 360         |
| Dysmenorrhea                    | 71 (53.79%)   | 360         |
| History of OCs                  | 62 (44.6%)    | 360         |
| Chief symptoms                  |            |             |
| Abnormal uterine bleeding       | 78 (43.58%)   | 360         |
| Hirsutism                       | 25 (13.97%)   | 360         |
| Acne                            | 14 (7.82%)    | 360         |
| Pelvic pain                     | 2 (1.12%)     | 360         |
| Amenorrhea                      | 53 (29.61%)   | 360         |
| Total T (nmol/L)                | 75.85 ± 43.8  | 360         |
| Free T (pg/mL)                  | 2.25 ± 1.18   | 360         |
| 17-OHP (ng/mL)                  | 1.51 ± 0.56   | 360         |
| DHEAS (μg/dL)                   | 227.23 ± 108.71 | 360     |
| SHBG (nmol/L)                   | 50.50 ± 40.73 | 360         |
| FAI                             | 262.37 ± 332.08 | 360    |
| FSH (mlu/mL)                    | 4.36 ± 1.37   | 360         |
| E2 (pg/mL)                      | 74.40 ± 35.42 | 360         |
| AMH                             | 11.54 ± 6.14  | 360         |
| Cholesterol (mg/dL)             | 181.75 ± 44.62 | 360    |
| TG (mg/dL)                      | 114.45 ± 77.19 | 360   |
| HDL (mg/dL)                     | 63.98 ± 20.69 | 360         |

21 days or more than 45 days. Only post-menarchal subjects were selected.

Study subjects were classified into four groups based on the Korean Society for the Study of Obesity 2018 [9]: low body weight < 18.5 kg/m², normal body weight 18.5-22.9 kg/m², pre-obese 23 - 24.9 kg/m², and obese ≥ 25 kg/m².

Ultrasound was performed by one gynecologist in a temperature-controlled room (25 °C). Transabdominal scans and transrectal scans were performed at 3.75 and 7.5 MHz frequencies, respectively. PCOM was defined as > 12 pre-antral follicles measuring 2-9 mm in diameter and/or increased ovarian volume (> 10 mL) in at least one ovary. The measurements taken included those of ovarian diameter, follicle count, and endometrial thickness. Scanning of both ovaries was done in the longitudinal (D1), anteroposterior (D2), and transverse diameters (D3). The total volume was analyzed by applying the ellipsoid equation, which is D1 × D2 × D3 × 0.523 cm³. Ovarian area was checked by tracing the ovarian surface in ultrasound (cm²).

The authors performed hormonal evaluations of total testosterone, free testosterone, 17-OH-progesterone (17-OHP), dehydroepiandrosterone-sulfate (DHEAS), and sex hormone binding globulin (SHBG), FSH, E2, and AMH. Serum AMH was measured in duplicate using an ultrasensitive electrochemiluminescence immunoassay analyzer.

The relationship between serum androgen levels and menstrual cycle length and serum AMH levels was investigated by correlation analysis. Hyperandrogenism was defined biochemically by serum total testosterone concentration > 95 nmol/L, free testosterone concentration > 4.6 pg/mL (0-4.6 pg/mL), and DHEAS > 333 μg/dL (30-333). An enzyme-linked immunosorbent assay (ELISA) was used for the quantitative determination of testosterone in serum. The reagents and calibrators for the testosterone analysis were supplied and dichloromethane was used for organic solvent extraction prior to quantification. Sex hormone binding globulin (SHBG) was measured quantitatively in serum using an ELISA method and the reagents and calibrators were provided. Free androgen index (FAI) was calculated using the formula: testosterone × 10/SHBG.

Statistical analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA). Continuous vari-
able are presented as mean and standard deviation and tested by independent t-tests or Wilcoxon’s rank sum tests for the < 20-year-old age group and by ANOVA or the Kruskal-Wallis test for the hyperandrogenic group. Correlations of continuous variables with AMH levels were evaluated by Pearson correlation coefficients.

**Results**

One hundred eighty-one women were initially evaluated from January 2013 to January 2018, and 42 women were excluded based on the exclusion criteria and insufficient data. A total of 139 women were finally included in the study. The authors analyzed the clinical features of nulliparous women ages 15 to 30 years, who had shown PCOM and been visiting the Obstetrics and Gynecologic Department of a single university hospital.

The mean age of the women at diagnosis was 21.5 years (SD 3.6), the mean height was 161.2 cm (SD 5.97), the mean body weight was 60.3 kg (SD 14.3), and the mean BMI was 23.2 kg/m2 (SD 5.1). The average age at menarche was 13.8 years (SD 1.6). Irregular menstrual cycles were found in 128 (94.8%) women and 62 (44.6%) women had histories of contraceptive use. The main reasons for the hospital visits included abnormal uterine bleeding (n = 78, 43.6%), amenorrhea (n = 53, 29.6%), and hirsutism (n = 25, 13.9%). The mean total serum testosterone was 75.85 ± 43.8 nmol/L, the mean free testosterone was 2.25 ± 1.18 pg/mL, the mean DHEAS was 227.23 ± 108.71 ug/dL, the SHBG was 50.50 ± 40.73 nmol/L, and the mean AMH was 11.54 ± 6.14 (Table 1).

In ultrasound findings, the mean right ovarian area was 6.09 ± 1.75 cm², the mean right ovarian volume was 7.52 ± 3.36 cm³, and the mean number of right ovarian follicles was 6.18 ± 4.25. The mean left ovarian area was 5.56 ± 1.69 cm², the mean left ovarian volume was 6.7 ± 2.97 cm³, and the mean number of left ovarian follicles was 16.74 ± 4.35. The mean endometrial thickness was 0.62 ± 0.23 cm. Compared to women younger than 20 years, ovarian area and volume increased after age 20 without statistical significance and the number of follicles was significantly decreased after 20 years of age (right ovarian follicle number 18.00 ± 4.02, < 20-year-old; 16.34 ± 4.27, > 20-year-old; p = 0.0250; left ovarian follicle number 18.49 ± 4.18 < 20-year-old; 15.91 ± 4.2 > 20-year-old; p = 0.0030; Table 2). When the BMI was less than 25 kg/m², the ovarian area and volume increased with increasing BMI (BMI < 18.5 kg/m² /18.5-22.9 kg/m² /23-24.9 kg/m²: right ovarian area 5.27 ± 1.74 cm² /6.12 ± 1.79 cm² /6.83 ± 1.40 cm²: left ovarian area 4.65 ± 1.99 cm² /5.37 ± 1.58 cm² /6.15 ± 1.77 cm²), but ovarian area and volume was decreased in the obese group (BMI ≥ 25 kg/m²: right ovarian area 6.0 ± 1.75 cm²; left ovarian area 5.97 ± 1.54 cm²) compared to women with BMI less than 25 kg/m². There was a statistically significant increase in the number of follicles in the obese group compared to the normal weight group (Table 2). Total testosterone and HDL cholesterol had a statistically significant positive correlation with AMH (total testosterone: r = 0.2181, p = 0.0328; HDL: r = 0.2079, p = 0.0498). 17-OHP (r = 0.1566, p = 0.1297), DHEAS (r = 0.0879, p = 0.3869), SHBG (r = 0.1667, p = 0.1063), and

**Table 2. — Analysis of Ovarian Morphology According to Age, BMI**

| Subgroup | Subgroup BMI (kg/m²) |
|----------|----------------------|
| < 20 years old | ≥ 20 years old | p-value(1) | 18.5-22.9(2) | 23-24.9(3) | ≥ 25(4) | p-value(2) |
| Rt. ov area (cm²) | 6.09 ± 1.75 | 6.06 ± 1.69 | 6.10 ± 1.79 | 0.8976 | 5.27 ± 1.74 | 6.12 ± 1.79 | 6.83 ± 1.40 | 6.0 ± 1.75 | 0.0455(b) |
| Rt. ov volume (cm³) | 7.52 ± 3.36 | 7.13 ± 3.29 | 7.71 ± 3.39 | 0.231 | 6.23 ± 3.01 | 7.43 ± 2.76 | 9.10 ± 4.42 | 7.50 ± 3.69 | 0.1582(b) |
| Rt. Follicle | 16.88 ± 4.25 | 18.00 ± 4.02 | 16.34 ± 4.27 | 0.0250 | 13.57 ± 2.38 | 17.34 ± 4.19 | 15.63 ± 5.12 | 17.61 ± 3.96 | 0.0056(c) |
| Lt. ov area(cm²) | 5.56 ± 1.69 | 5.39 ± 1.62 | 5.65 ± 1.72 | 0.4110 | 4.65 ± 1.99 | 5.37 ± 1.58 | 6.15 ± 1.77 | 5.97 ± 1.54 | 0.0417(c) |
| Lt. ov volume(cm³) | 6.7 ± 2.97 | 6.31 ± 2.45 | 6.89 ± 3.19 | 0.5207 | 5.05 ± 2.95 | 7.01 ± 3.06 | 7.20 ± 2.3 | 7.18 ± 2.91 | 0.0362(c) |
| Lt. Follicle | 16.74 ± 4.35 | 18.49 ± 4.18 | 15.91 ± 4.2 | 0.0030 | 14.46 ± 3.33 | 16.34 ± 4.23 | 16.11 ± 4.62 | 18.51 ± 4.29 | 0.0103(c) |
| Endometrium (cm) | 0.62 ± 0.23 | 0.61 ± 0.24 | 0.63 ± 0.23 | 0.3291 | 0.53 ± 0.27 | 0.61 ± 0.2 | 0.70 ± 0.26 | 0.65 ± 0.25 | 0.1214(c) |

oov - ovary
p-value (1): Independent t-test
1) Wilcoxon’s rank sum test
2) Kruskal-Wallis test
*p-value < 0.05, statistically significant
**p-value < 0.05, statistically significant, post hoc method by Bonferroni (1) vs. (2)
***p-value < 0.05, statistically significant, post hoc method by Bonferroni (1) vs. (3)
****p-value < 0.05, statistically significant, post hoc method by Bonferroni (1) vs. (4)
*****p-value < 0.05, statistically significant, post hoc method by Bonferroni (2) vs. (3)
******p-value < 0.05, statistically significant, post hoc method by Bonferroni (2) vs. (4)
*******p-value < 0.05, statistically significant, post hoc method by Bonferroni (3) vs. (4)

Clinical presentation, hormonal profiles in nulliparous Korean women...
In the analysis of AMH, there was a statistically significant positive correlation between AMH and both ovarian areas (right r = 0.3801, p < 0.0001; left r = 0.2478, p = 0.0071), ovarian volume (right r = 0.2188, p = 0.0173; left r = 0.2255, p = 0.0141), and ovarian follicles (right r = 0.4472, p < 0.0001; left r = 0.2458, p = 0.0111).

The patients were grouped by their total testosterone and free testosterone values for further analysis. Total testosterone > 95 nmol/L and free testosterone > 3.09 pg/mL were group A (n = 9), total testosterone > 95 nmol/L (n = 14) were group B, and free testosterone > 3.09 were classified as group C (n = 14). Group D was comprised of patients with normal total testosterone and free testosterone levels. Free testosterone, 17-OHP, DHEAs, SHBG, and FSH were significantly higher in patients with hyperandrogenism (A, B, and C) than in the normal group (D).

Both ovarian follicle counts were significantly higher in the A, B, and C groups than in the D group (Table 4). Thirty-seven women (26.6%) were hyperandrogenic. There was no correlation between hyperandrogenism and AMH levels, ovarian area, volume, or follicle numbers.

Discussion

PCOM is a frequent finding (30%) in ultrasound images in the general population [10]. It was found in the ultrasonograms of young nulliparous women who visited the Obstetrics and Gynecology Department at this institution for various reasons.

A previous study found that PCOM in healthy adult pre-menopausal women was not related to metabolic variables (FSH, E2, AMH, testosterone etc.), although the serum AMH and androgen concentrations of these women were often slightly higher than those of women without PCOM [11]. PCOM did not predict the future development of PCOS, and even within PCOS patients, not all women meeting the PCOM criteria at baseline fulfilled such criteria later in life [12].

The characterization of PCOM in the asymptomatic general population is unknown at present. However, it is possible that isolated PCOM may be a precursor of ovarian dysfunction in some women. Therefore, clinical and possibly ultrasonograph and/or AMH follow-up of these women may be a reasonable approach [2]. There is little evidence to suggest that the sole presence of PCOM results in any significant risk to reproductive health in the absence of other symptoms. One expert argued that PCOM was associated with subtle abnormalities that are characteristic of a polycystic ovary, mainly, increased serum AMH levels [13].

In the present study, the mean total testosterone, free testosterone, DHEAs, and AMH levels were within normal ranges in 131 women with PCOM features, but hyperandrogenism was found in 26.6% of these women, and so PCOM-specific features were not surrogate markers for the diagnosis of PCOS.

Irregular menstrual cycles were found in 94.8%, abnormal uterine bleeding in 43.6% and biochemical hyperandrogenism in 26.6% of the women with PCOM features, therefore, follow-up to assess the development of PCOS in these women is necessary.

The utility of ultrasound to define the ovarian morphology in adolescents is limited by the transabdominal image quality. Poor ovarian imaging, especially in obese girls, precludes the differentiation between polycystic and multi-follicular ovaries [14]. Ideally, transvaginal ultrasound should be performed to optimize image resolution, particularly in obese patients, such as those studied here and commonly found in patients with PCOS. Transvaginal ultrasounds, however, are often unobtainable in adolescents due to their young age [15]. In the present study, transabdominal or transrectal ultrasounds were performed in women who could not undergo examination by transvaginal ultrasound.

When the relationship between body weight, ovarian area and ovarian volume was assessed in women with PCOM, we observed that ovarian area and ovarian volume in women with BMI < 25 kg/m² increased with increasing BMI. However, in with BMI ≥ 25 kg/m², the ovarian area and ovarian volume were decreased, and the measurement of ovarian area and ovarian volume was difficult in obese women with PCOM. The thickness of the abdominal wall and adipose tissue makes ultrasound examination difficult and insufficient in obese women. Because there are few study related ovarian morphology with change of BMI, further study is needed.

In the present study, the number of ovarian follicles was
higher in the obese group than in the normal weight group. This suggests that there were more follicles in the obese group than in the normal weight group and that ovulation may not have occurred properly in this group and likely resulted in menstrual irregularities.

The present study demonstrated that serum AMH positively correlated with ovarian volume, follicle number in nulliparous women with PCOM. Ovarian volume comprises follicular and stromal volumes.

The most important finding of this study is the close and similar relationship between serum AMH and antral follicle count in women with PCOM in Korean nulliparous women, hyperandrogenism must be studied at different aspects.

The cause of increased AMH production in PCOS is unclear; however, the increase in AMH concentration is largely attributed to the increase in production of AMH by each follicle and not just a consequence of increased follicle numbers [16, 17].

Positive correlations have previously been reported for androstenedione and testosterone or the FAI in women with PCOS [18]. In the present study, the authors found little relationship between total testosterone and serum AMH levels but there was no correlation between free testosterone, 17-OHP, DHEAS, SHBG, FSH, E2, and AMH levels.

An increased level of AMH was found in women with PCOM features and there was a strong positive correlation between AMH levels and ovarian follicles in women with PCOM feature. The cause of high levels of AMH in PCOM featured women is unknown, and it may be secondary to the disruption in folliculogenesis, thus leading to an excessive accumulation of growing follicles [5, 19].

This is the first study to evaluate the characteristics of polycystic ovary in association with hyperandrogenism in Korean nulliparous women. There are a number of caveats that must be observed in interpreting the results presented in this paper. Firstly, data of women with normal menstrual cycles were not investigated and there was a possibility that selection bias resulted from using the patients’ symptoms when they visited the university hospital. Secondly, study population size was small and the study was limited by its retrospective design.

In conclusion, this study confirmed that AMH levels can be applied alongside the existing criteria to diagnose PCOM. AMH levels may be more reflective of ovarian morphology, rather than hyperandrogenism. Long-term follow-up of a large study cohort is warranted, to clarify whether PCOM by itself, is part of the PCOS phenotype or whether it may be present in women of all ages as a subclinical form of PCOS. Such a study should also investigate possible long-term health risks associated with isolated PCOM. AMH has the potential to increase our understanding of ovarian pathophysiology and to further guide the clinical management of a broad range of conditions. If accompanied by other symptoms, the development of PCOS should be investigated more extensively.
Abbreviations

PCOS, Polycystic ovarian syndrome; PCOM, Polycystic ovarian morphology; DHEAS, dehydroepiandrosterone-sulfate; SHBG, sex hormone binding globulin; FAI, free-androgen-index; FSH, follicle stimulating hormone; AMH, anti-Müllerian hormone.

Acknowledgments

The authors would like to thank the individuals who participated in this study, for their time and contribution to this important field of research.

Conflict of Interest

The authors declare no conflict of interest.

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