



Influence of combined oral contraceptives on polycystic ovarian morphology-related parameters in Korean women with polycystic ovary syndrome

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Objective

This study aimed to assess the effect of combined oral contraceptives (COCs) on polycystic ovarian morphology (PCOM) and serum anti-Müllerian hormone (AMH) levels in Korean women with polycystic ovary syndrome (PCOS).

Methods

This university hospital study enrolled 36 Korean women who were newly diagnosed with PCOS based on the Rotterdam criteria and were treated with COCs for at least 1 year. We retrospectively evaluated the ovarian volume and number of antral follicles using ultrasonography and assessed serum AMH levels at baseline and after 1 year of COC treatment.

Results

Significant decreases in ovarian volume and antral follicle count were observed after 1 year of COC treatment. Compared to baseline, serum AMH levels were significantly decreased after 1 year.

Conclusion

COC treatment significantly affects ultrasound-assessed PCOM and serum AMH levels of patients with PCOS.

Keywords: Anti-Müllerian hormone; Combined oral contraceptives; Polycystic ovarian morphology; Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 8–13% women of reproductive age [1,2]. Common clinical characteristics include chronic anovulation, hyperandrogenism (hyperandrogenemia or clinical hyperandrogenism), and polycystic ovaries on ultrasonography. Infertility caused by chronic ovulatory dysfunction, abnormal gonadotropin secretion [3], and metabolic disturbances, such as central obesity, dyslipidemia, insulin resistance, and hyperinsulinemia, can be simultaneously encountered in PCOS [4].

The Rotterdam criteria have been widely used for the diagnosis of PCOS [5]. PCOS is diagnosed in women with at least 2 of the following: oligo-anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) on ultrasound (≥ 12 follicles measuring 2–9 mm in diameter in at least 1 ovary, and/or increased ovarian vol-

ume to >10 cm³) after the exclusion of androgen excesses.

Anti-Müllerian hormone (AMH), produced in the granulosa cells of small antral and preantral follicles, is a type of transforming growth factor β [6]. AMH plays a critical role in

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chronic anovulation by interrupting the initiation of primordial follicular growth [7] and promoting the arrest of follicular development [8]. AMH was recently recognized as a useful clinical marker for evaluating PCOS [9] and is considered promising for the accurate detection of PCOM [10].

Combined oral contraceptives (COCs), along with lifestyle modifications, are recommended for the primary management of PCOS to treat clinical symptoms such as irregular menstrual cycles, hirsutism, weight gain, and associated lipid, glucose, and testosterone disturbances [10]. However, in previous studies, treatment effects varied in association with the heterogeneous composition of COCs, treatment duration, symptom severity/phenotype, and accessibility of the treatment regimen [11-14]. Reports on the effects of COCs on PCOM and AMH among Korean women are lacking.

Thus, we aimed to examine the effect of COC treatment on PCOM and serum AMH levels in Korean patients with PCOS.

Materials and methods

1. Patient population and study design

This retrospective study included Korean women aged 18–35 years who were diagnosed with PCOS during their first visit to Inje University Haeundae Paik Hospital between June 2010 and December 2014; these women were followed up with transvaginal (TV-US) or transrectal ultrasound (TR-US) and serum AMH levels after 1 year of COC treatment. PCOS was diagnosed according to the Rotterdam criteria [5]. PCOS is diagnosed in women with at least 2 of the following: oligo-anovulation, clinical and/or biochemical hyperandrogenism, and PCOM on ultrasonography; other pathologic conditions such as non-classical congenital adrenal hyperplasia, androgen-producing tumors, hyperprolactinemia, Cushing's syndrome, and thyroid dysfunction were ruled out. Oligomenorrhea is defined as an interval of >35 days between menstrual cycles, while amenorrhea is defined as an interval of >90 days between menstrual cycles. In our trial, clinical hyperandrogenism was defined as the presence of hirsutism based on a Ferriman-Gallwey score of >6, modified for Korean women by Kim et al. [15]; biochemical hyperandrogenism was defined as a serum testosterone level exceeding 95% confidence limits, as reported by Chae et al. [16] (total testosterone level >0.68 ng/mL and/or free testosterone level >1.72 pg/mL). PCOM was defined as follows: ≥ 12

follicles measuring 2–9 mm in diameter in each ovary and/or an ovarian volume of >10 mL on TV-US or TR-US. Exclusion criteria were as follows: prior ovarian surgery, suspected ovarian malignancy, or known contraindications to estrogen therapy and use of oral contraceptives, ovulation-inducing drugs, glucocorticoids, or anti-androgenic agents, which can affect the hypophysis-pituitary-ovarian axis in the 6 months preceding the diagnosis. Finally, 36 patients were included in our study. All patients were given a 24-day regimen of COCs containing ethinylestradiol (EE) 20 μ g and drospirenone (Yaz[®]) 3 mg.

2. Assessment of ovarian volume and antral follicle count

All subjects were followed up with TV-US or TR-US to assess ovarian volume and antral follicle count. The TV-US or TR-US examination was performed using a Voluson S7 device (General Electric Systems, Seongnam, Korea) with a 7-MHz transvaginal probe. The baseline ultrasound was conducted at the early follicular phase, and the ultrasound after 1 year of treatment was performed during the pill-free interval (7–21 days) of the COC treatment. All the ultrasound examinations were conducted by the same reproductive endocrinologist in accordance with the international ultrasound definitions of PCOM [17]. The number of antral follicles measuring 2–9 mm in diameter was calculated using a continuous scanning method for each ovary from the inner to outer margins of a longitudinal cross-section. Ovarian volume was calculated according to a simplified formula for a prolate ellipsoid ($0.5 \times \text{length} \times \text{width} \times \text{thickness}$) [17]. Total ovarian volume (TOV) was calculated as the sum of the volume of the right ovary (ROV) and left ovary (LOV), and total antral follicle count (TFC) was calculated as the sum of the follicle count of the right ovary (RFC) and left ovary (LFC).

3. Measurement of serum anti-Müllerian hormone levels

Blood samples were collected in tubes without anticoagulants on the day of ultrasound examination, and the biochemical parameters of the serum were measured. Serum AMH levels were determined using an AMH Gen II assay (Beckman Coulter Inc., La Brea, CA, USA).

4. Statistical analysis

Data are expressed as mean \pm standard deviation and ana-

lyzed using SPSS version 25.0 (SPSS, Chicago, IL, USA). A paired samples *t*-test was used to compare parameters related to ovarian follicle count (TFC, RFC, and LFC), ovarian volume (TOV, ROV, and LOV), and AMH levels at baseline and after 1 year of treatment. Statistical significance was set at $P < 0.05$.

Results

Baseline clinical characteristics are shown in Table 1. Table 2 shows that the baseline ultrasound parameters related to PCOM were significantly decreased after 1 year of COC treatment. There was a significant decrease in TFC from baseline (73.83 ± 43.14) to 1 year (44.11 ± 28.09) (40.3% decrease, $P < 0.001$). In addition, TOV decreased significantly after 1 year of treatment (from 24.57 ± 8.39 to 14.13 ± 5.92 cm^3 ; $P < 0.001$). Serum AMH levels were decreased significantly from 11.09 ± 4.6 ng/mL at baseline to 6.45 ± 3.29 ng/mL after 1 year of COC treatment ($P < 0.001$).

Discussion

PCOM is 1 of 3 items needed for diagnosis of PCOS. The

2 cardinal features of PCOM include increases in ovarian volume and AFC levels. The AMH level is correlated with the number of follicles that are 2–5 mm in diameter [18]; serum AMH level is useful for assessing PCOM in patients with PCOS. COCs are recommended as primary treatment for chronic anovulation and hyperandrogenism in PCOS [10]. However, adequate research on the effects of COCs on PCOM in women with PCOS is lacking, and to the best of our knowledge, no such research has been performed among Korean women. We found a significant decrease in baseline TFC, TOV, and AMH values after 1 year of COC treatment in Korean patients with PCOS.

Several studies have investigated whether COCs can modulate PCOM in patients with PCOS [13,19–25]. According to Mes-Krowinkel et al. [19], the mean ovarian volume, mean ovarian follicle count, and AMH level remarkably decreased in patients using COCs than in patients who had never used COCs after correction for confounding variables such as body mass index, age, waist-to-hip ratio, previous pregnancy, infertility treatment, and ethnicity. Another study [20] reported that ovarian volume (ROV, LOV, and TOV), ovarian follicle count (RFC, LFC, and TFC), and AMH level were significantly decreased after 3 months of COC treatment. The authors suggested that the AMH level decreased due to COC-induced suppression of ovarian function. They used cyproterone acetate (CPA) 2 mg/EE (Diane 35) 35 μg ; however, per current recommendations [10], this should not be first-line treatment because of adverse effects such as venous thromboembolism. Moreover, the AMH assay kits used

Table 1. Baseline patient characteristics (n=36)

| Characteristics | Participants |
|-----------------------|--------------|
| Age (yr) | 25.03±5.35 |
| Height (cm) | 161.62±6.00 |
| Body weight (kg) | 56.18±13.24 |
| Body mass index | 21.36±4.04 |
| Waist to hip ratio | 0.77±0.06 |
| TFC | 73.83±43.14 |
| RFC | 39.31±21.54 |
| LFC | 34.53±22.35 |
| TOV (cm^3) | 24.57±8.39 |
| ROV (cm^3) | 13.65±5.84 |
| LOV (cm^3) | 10.91±4.11 |
| AMH level (ng/mL) | 11.09±4.61 |

Data was expressed as mean±standard deviation.

TFC, total follicle count; RFC, right ovarian follicle count; LFC, left ovarian follicle count; TOV, total ovarian volume; ROV, right ovarian volume; LOV, left ovarian volume; AMH, anti-Müllerian hormone.

Table 2. Serial changes in ultrasound parameters of ovarian size and serum anti-Müllerian hormone levels (n=36)

| Parameters | Basal | Post 1 year | P-value ^{a)} |
|-----------------------|-------------|-------------|-----------------------|
| TFC | 73.83±43.14 | 44.11±28.09 | <0.001 |
| RFC | 39.31±21.54 | 23.19±14.92 | <0.001 |
| LFC | 34.53±22.35 | 20.91±13.78 | <0.001 |
| TOV (cm^3) | 24.57±8.39 | 14.13±5.92 | <0.001 |
| ROV (cm^3) | 13.65±5.84 | 7.53±3.43 | <0.001 |
| LOV (cm^3) | 10.91±4.11 | 6.59±3.07 | <0.001 |
| AMH level (ng/mL) | 11.09±4.61 | 6.45±3.29 | <0.001 |

Data was expressed as mean±standard deviation.

TFC, total follicle count; RFC, right ovarian follicle count; LFC, left ovarian follicle count; TOV, total ovarian volume; AMH, anti-Müllerian hormone; LOV, left ovarian volume; ROV, right ovarian volume.

^{a)}*P*, paired samples *t*-test.

differed from those in our study. Plouvier et al. [21] reported a significant decrease in follicle numbers per ovary and AMH levels after a 3-month trial of COCs. Fábregues et al. [22] reported significant TFC reductions after 6 months of COC use, with a significant positive correlation between TFC and AMH level ($\rho=0.92$ and 0.88 ; $P=0.01$ and 0.004 , respectively). They used desogestrel 2 mg/EE 20 μg as COC therapy in their research. Another study [23] reported that AMH, ROV, and LOV were significantly decreased after 6 months of COC use and that there was a significant correlation between LOV and AMH level at baseline and those after 6 months of treatment ($\rho=0.336$ and 0.310 ; $P=0.018$ and 0.034 , respectively). All patients in this study were adolescents with PCOS aged 13–17.5 years taking COCs containing drospirenone 3 mg/EE 30 μg .

Our results were not comparable to those of 2 previous studies. Panidis et al. [24] reported changes in AMH levels in 2 other COC treatment groups (CPA 2 mg/EE 35 μg and drospirenone 3 mg/EE 2 μg) at 3 time points (baseline, 3 months, and 6 months). AMH level was significantly decreased in the CPA 2 mg/EE 35 μg group, but not in the drospirenone 3 mg/EE 2 μg group. However, the definition of PCOS in that study was based on the 1990 National Institutes of Health criteria for PCOS, and we used a different AMH assay kit in our study. Somunkiran et al. [25] reported that TFC and TOV, but not AMH level, were decreased after 6 months of therapy. However, the COC formula (CPA 2 mg/EE 35 μg) and AMH assay kit differed from those in our study.

PCOS exhibits an abnormal gonadotropin secretion pattern. The increasing frequency of pulsatile gonadotropin-releasing hormone secretion at the level of the hypothalamus accelerates transcription of the β -subunit of luteinizing hormone (LH) more than that of the same subunit of follicle-stimulating hormone (FSH) [26] and increases the amplitude and pulse frequency of LH secretion in the pituitary [27]. As a result, an increase in the LH/FSH ratio and serum LH level is observed in patients with PCOS. Normal ovulation requires the coordinated and synchronized interaction of LH, FSH, insulin-like growth factor, and AMH. However, in PCOS, inappropriate gonadotropin secretion inhibits the selection of dominant follicles and causes follicular arrest at an early antral stage [2]. Consequently, PCOM and AMH levels increase. Chun [28] proposed that TOV and TFC are significantly correlated with the LH/FSH ratio and serum LH level; in addition, changes

in PCOM findings could reflect post-treatment changes in gonadotropin release. Excess AMH production might be associated with an increased antral follicle count caused by intra-ovarian androgen overabundance [24]. Drospirenone-containing COCs may decrease serum androgen and gonadotropin levels; these combined effects of COCs could contribute to changes in PCOM and AMH levels in patients with PCOS.

Our study showed that COC treatment can improve PCOM (ovarian volume and follicle counts) and AMH levels, although the mean values in our participants still satisfied the diagnostic criteria of PCOM after 1 year of treatment. This result is in agreement with that reported by Mes-Krowinkel et al. [19] and may indicate that PCOM is relatively stable during COC treatment and could be a reliable marker for PCOS.

Insulin resistance contributes to the pathology of PCOS and is a cause of abnormal steroidogenesis within the ovaries [2,27]. Several studies have assessed whether AMH levels affect insulin resistance. According to Chun [29], patients with PCOS and a high AMH level (≥ 10.0 ng/mL) had a significantly higher 1-hour postprandial glucose (PPG1) level than those with an AMH level of < 10 ng/mL. PPG1 is considered a better predictor of the risk of developing type 2 diabetes mellitus than 2-hour postprandial glucose level [30]. Nardo et al. [31] reported that AMH levels increased with insulin levels based on the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Skalba et al. [32] reported a significant correlation of serum AMH and total or low-density lipoprotein cholesterol levels with HOMA-IR and a significant negative correlation between high-density lipoprotein cholesterol and AMH levels. According to a previous study [33], total cholesterol level showed a positive correlation with the LH/FSH ratio. However, other researchers reported no correlation of AMH and PCOM with insulin-linked metabolic parameters [34-36].

In our research, PCOM was defined according to the Rotterdam criteria [5]. Based on newly revised recommendations in 2018 [10], however, the diagnostic criteria for PCOS have changed to some extent, especially with regard to ultrasound and PCOM. The diagnostic threshold for PCOM in either ovary has been revised as follows: ≥ 20 follicles per ovary and/or ovarian volume of ≥ 10 mL in either ovary using an endovaginal ultrasound transducer with a frequency bandwidth that includes 8 MHz after ensuring that the corpus luteum,

cysts, or dominant follicles are absent. Based on the newly revised recommendations [37] for determining the number of follicles per ovary, the authors analyzed 11 studies including 2,961 adult patients, and the data suggested optimal sensitivity and specificity at >19 follicles per ovary. They noted that the limitations of their work included the heterogeneous population (patients with and without PCOS) and use of 95% cutoff values to define abnormality. Further studies based on the revised 2018 recommendations are warranted.

The limitations of our study include its retrospective design and small sample size. Most patients in our study visited our hospital for oligo-anovulation or infertility rather than symptoms associated with hyperandrogenism. Therefore, the number of PCOS patients with clinical and/or biochemical hyperandrogenism might be lower in our study group than in the general PCOS patient population.

Our study was designed to compare PCOM and AMH levels at baseline and after 1 year of COC treatment in contrast with other studies that had a follow-up duration of ≤6 months.

In conclusion, our study showed that COC treatment significantly influences both ultrasound and serum parameters of PCOM and PCOS. To the best of our knowledge, this is the first study to investigate the effects of COCs on PCOM-related ultrasound and serum parameters among Korean women. Undoubtedly, the purpose of COC treatment in women with PCOS is managing hyperandrogenism and/or irregular menstrual cycles [37] and not to cure PCOS. In this respect, the clinical significance of the effect of COCs on PCOM in women with PCOS remains unclear. Further prospective large-scale trials will help confirm these preliminary findings.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The study received approval from the Inje University Haeundae Paik Hospital Institutional Review Board (IRB No. 129792-2014-035).

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