Correlation of ovarian volume and clinical and laboratory parameters of PCOS in Korean patients

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Abstract

Background: The aim of this study is to analyze the correlation of ovarian volume and clinical and laboratory parameters of polycystic ovary syndrome (PCOS) in Korean women. Methods: Two hundred and thirty-three patients aged between 20 and 40 years with PCOS diagnosis between January 2014 and June 2020 at Pusan National University Hospital, Busan, Republic of Korea, were included to this retrospective observational study using previously recorded patient medical charts. PCOS was diagnosed according to the revised 2003 Rotterdam criteria. Laboratory tests including anti-mullerian hormone (AMH), prolactin, thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, free and total testosterone, dehydroepiandrosterone-sulfate (DHEA-S), 17-alpha-hydroxyprogesterone (17-OHP), HbA1C and insulin were conducted. Results: The correlation analysis showed that free testosterone (p = 0.006, r = 0.215), total testosterone (p < 0.001, r = 0.305), 17-OHP (p = 0.008, r = 0.203) and height (p = 0.008, r = 0.173) were statistically correlated with the total ovarian volume in overall PCOS patients. In these patients, serum AMH level was positively correlated with LH but negatively with body weight and body mass index (BMI). Conclusions: According to the results, the ovarian volume, quantified by ultrasonographic measurements, was significantly related to the increasing serum levels of free testosterone, total testosterone and 17-OHP in Korean PCOS patients.

Keywords: Ovarian volume; Polycystic ovarian syndrome; Metabolic parameters

1. Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent reproductive disorder which causes significant health consequences for women, such as infertility and other endocrine disorders requiring more sophisticated management than the non-PCOS population, thus impairing quality of life and increasing morbidity [1,2]. The Rotterdam criteria, established as the one of diagnostic criteria of PCOS, are now internationally accepted, with different phenotypes recognized with varying clinical presentations and risk profiles. The Rotterdam diagnosis for PCOS requires two of the following features: oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries [3]. According to the Rotterdam diagnostic criteria, the prevalence of PCOS in adolescents varies between a minimum of 3% and a maximum of 26%. The estimated prevalence of PCOS in Korean women has been reported as 5.85% [4].

In 2003, ultrasonographic evidence of polycystic ovaries was included as the third diagnostic criterion, since there was sufficient evidence worldwide supporting polycystic ovary morphology (PCOM) as a consistent finding in women with clinical and endocrine features of PCOS [5]. The possible explanation of high anti-mullerian hormone (AMH) and increased ovarian volume has been implied as the excessive number of small follicles present in polycystic ovaries, according to the study of Giampaolino et al. [6]; recently, one study has suggested that ovarian volume is significantly higher in metabolic syndrome patients comorbid with PCOS compared with non-PCOS metabolic patients [6,7]. The possible mechanism of increasing ovarian volume is described as follows; androgens are almost always detected at high levels in PCOS patients due to ovarian stromal hypertrophy, and hyperinsulinemia increases the production of androgens by having mitogenic effect on ovarian theca cells [8].

However, the relationship between ovarian volume and parameters of PCOS is inconclusive. Reid et al. [9] have reported that ovarian volume is an important factor associated with metabolic risk in women with PCOS. In contrast, Han et al. [10] have concluded that the ovarian volume does not seem to be related to patient weight, height, body mass index and other hormonal parameters except AMH level. Such controversies need to be stabilized in urgent order to provide the PCOS patients with more efficient, patient-specific therapeutic strategies endorsing critical metabolic aspects of the disease.

The aim of this study is to analyze the correlation of ovarian volume and clinical and laboratory parameters of PCOS in Korean women.
2. Materials and methods

2.1 Patient characteristics

Out of 282 patients with previously diagnosed PCOS between January 2014 and June 2020 at Pusan National University Hospital, Busan, Republic of Korea, a total of 233 patients aged between 20 and 40 years with PCOS diagnosis satisfying the revised 2009 Rotterdam criteria were included in this study. This study was a retrospective observational study using previously recorded patient medical charts.

2.2 Diagnostic criteria of PCOS and classification of patient groups

For PCOS diagnosis, revised 2003 Rotterdam criteria were adopted. Revised 2003 Rotterdam criteria were defined as follows: (1) oligo- and/or anovulation, clinically expressed as irregular menstruation (IM); (2) clinical and/or biochemical signs of hyperandrogenism (HA); and (3) polycystic ovary (PCO) on gynecological ultrasonography, after the exclusion of other etiologies including congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing’s syndrome [11]. According to the criteria, diagnosed PCOS patients were further classified into four subgroups: (1) HA + IM + PCO; (2) HA + IM; (3) HA + PCO; and (4) IM + PCO.

Each component of the Revised 2003 Rotterdam criteria was defined to contain the following clinical manifestations after thorough clinical history taking and physical examination, respectively, according to the international evidence-based guideline for PCOS developed by renowned organizations globally in 2018 [12]. First, irregular menstruation cycles due to oligo- and/or anovulation were allotted when the cycle was shorter than 21 or longer than 35, when the total number of cycles was lower than 8 per year, or when more than 90 days for any one cycle was experienced. Second, clinical hyperandrogenism included hirsutism, alopecia and acne: for hirsutism, modified Ferriman Gallway score with cut-off score of ≥6 was used; for alopecia — preferably termed female pattern hair loss (FPHL) — the Ludwig visual score was used; and for acne, despite the absence of universal agreement on visual assessments for its evaluation, the term “acne vulgaris” (AV) was applied when the patient had a pilosebaceous unit that causes noninflammatory comedones, inflammatory lesion containing red papules, pustules or nodules, and varying degrees of scarring [12–15]. Lastly, PCOM was given when the number of visible follicles was 20 or higher and/or when the ovarian volume was 10 mL or larger on either ovary, without corpora luteal cysts or dominant follicles, using gynecological ultrasonography, preferably by transvaginal approach if not otherwise contraindicated. When contraindicated, transrectal approach was used.

2.3 Measurement of ovarian volume

Ovarian volume was measured using a 5–9 MHz transvaginal transducer or transrectally (Voluson E6 General Electric, Milwaukee, Wauwatosa, WI, USA). The simplified formula adopted was as follows: 0.5 × length × width × thickness.

3. Anthropometric measurements and laboratory parameters

Each patient’s height and body weight were measured individually, and body mass index (BMI) was calculated as the patient’s weight in kilograms divided by her height in meters squared.

After 8 hours of overnight fasting, blood samplings were conducted for the assay of serum level of AMH, prolactin, thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, free testosterone, total testosterone, dehydroepiandrosterone-sulfate (DHEA-S), 17-alpha-hydroxyprogesterone (17-OHP), HbA1C and insulin. Assay for serum level of AMH was performed using an anti-Mullerian hormone/Mullerian inhibiting substance enzyme immune assay (AMH/MIS EIA) kit (Beckman Coulter, Paris, France), and serum prolactin levels were measured by an immunoradiometric assay (IRMA, Brussels, Belgium). Serum TSH was measured using Coat-A-Count TSH IRMA Kit (SIMENS, Dublin, Ireland), and serum FSH, LH, estradiol, free and total testosterone and 17-OHP were assessed using according ImmunoChemTM Coated Tube Radioimmunooassay Kits (MP Biomedical, Santa Ana, CA, USA). Assay for serum DHEA-S was performed using DHEA-Sulfate RIA kit (Beckman Coulter, Brea, CA, USA). HbA1c was evaluated using Roche Modular DP with enzymatic colorimetric method (Tokyo, Japan), and finally insulin was measured using Coat-A-Count® Inulin Kit by solid-phase 125I radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA).

5. Statistical analysis

All statistical data was organized into a computerized database. The statistical analysis was performed SPSS ver. 22 (IBM Co., Armonk, NY, USA). A multivariate analysis was performed to compare basal patient characteristics, ovarian volumes, clinical and hormonal parameters of 4 independent subgroups using one-way ANOVA and Bonferroni post-hoc test; for categorical variables, Chi-square test or Fisher’s test was used, and for continuous variables, Independent t-test or Wilcoxon rank-sum test was used. Pearson correlation parameters analysis was used for correlation between total ovarian volumes and the patients’ clinical and laboratory parameters. Statistical significance was indicated with p-values < 0.05.
6. Results

The overall characteristics of patients and subgroups are presented in Table 1. The following parameters were considered statistically significant: first, sonographic findings, including right ovarian volume ($p = 0.001$), left ovarian volume ($p = 0.041$), total ovarian volume ($p < 0.001$); second, several hormonal parameters, including free testosterone ($p < 0.001$), total testosterone ($p < 0.001$), DHEA-S ($p < 0.001$) and 17-OHP ($p < 0.012$); last, clinical parameters implying hyperandrogenism, including hirsutism ($p < 0.001$), acne ($p < 0.001$) and alopecia ($p < 0.001$).

The correlation analysis for the total ovarian volume is shown in Table 2. Free testosterone ($p = 0.006$, $r = 0.215$), total testosterone ($p < 0.001$, $r = 0.305$), 17-OHP ($p = 0.008$, $r = 0.203$) and height ($p = 0.008$, $r = 0.173$) were statistically correlated with the total ovarian volume in PCOS patients overall. In addition, in the group with both hyperandrogenism and irregular menstruation (HA-IM subgroup), total testosterone was significantly correlated with the patient’s total ovarian volume ($p = 0.039$, $r = 0.346$).

Table 3 shows the results of correlation analysis for serum AMH level and clinical and laboratory parameters of PCOS in overall patients and as well as in each subgroup. In the PCOS patients overall, serum AMH level was positively correlated with LH but negatively with body weight and BMI. Similar pattern of results was also found in the IM-PCO subgroup.

7. Discussion

In the present study, the ovarian volume measured by ultrasonography was positively related to serum levels of free testosterone, total testosterone and 17-OHP in PCOS patients; especially, free testosterone, total testosterone and DHEA-S were significantly different among the subgroups.
Table 2. Correlation analysis for total ovarian volume and parameters of PCOS according to the subgroups.

| Subgroup         | Total (n = 233) | HA-IM-PCO (n = 75) | HA-IM (n = 60) | HA-PCO (n = 4) | IM-PCO (n = 94) |
|------------------|----------------|--------------------|----------------|---------------|----------------|
|                  | r   | p    | r   | p    | r   | p    | r   | p    | r   | p    | r   | p    | r   | p    | r   | p    |
| Free T (pg/mL)   | 0.215 | 0.006 | −0.123 | 0.329 | 0.192 | 0.213 | 0.891 | 0.299 | 0.204 | 0.169 |
| Total T (pg/mL)  | 0.305 | <0.001 | 0.062 | 0.626 | 0.346 | 0.039 | −0.985 | 0.111 | 0.243 | 0.107 |
| DHEA-S (ug/mL)   | −0.032 | 0.703 | −0.250 | 0.052 | 0.234 | 0.190 | 0.817 | 0.183 | −0.155 | 0.304 |
| HA1c (%)         | 0.131 | 0.151 | 0.126 | 0.410 | 0.161 | 0.370 | 0.925 | 0.058 | 0.723 |
| 17-OHP (ng/mL)   | 0.203 | 0.008 | 0.040 | 0.746 | 0.036 | 0.812 | −0.113 | 0.877 | 0.204 | 0.147 |
| BW (kg)          | 0.112 | 0.087 | 0.099 | 0.398 | 0.086 | 0.514 | 0.700 | 0.300 | −0.070 | 0.505 |
| Age              | −0.082 | 0.214 | −0.022 | 0.850 | −0.129 | 0.326 | −0.764 | 0.236 | −0.098 | 0.346 |
| HT (m²)          | 0.173 | 0.008 | 0.107 | 0.362 | 0.094 | 0.473 | −0.351 | 0.649 | 0.019 | 0.857 |
| BMI (kg/m²)      | 0.064 | 0.329 | 0.056 | 0.633 | 0.062 | 0.636 | 0.586 | 0.414 | −0.077 | 0.462 |

HA, hyperandrogenism; IM, irregular menstruation; PCO, polycystic ovaries; T, testosterone; DHEA-S, dehydroepiandrosterone-sulfate; 17-OHP, 17-alpha-hydroxyprogesterone; BW, body weight; HT, height; BMI, body mass index.

Table 3. Correlation analysis for serum AMH level and other parameters of PCOS according to the subgroups.

| Subgroup         | Total (n = 233) | HA-IM-PCO (n = 75) | HA-IM (n = 60) | HA-PCO (n = 4) | IM-PCO (n = 94) |
|------------------|----------------|--------------------|----------------|---------------|----------------|
|                  | r   | p    | r   | p    | r   | p    | r   | p    | r   | p    | r   | p    | r   | p    |
| PRL (ng/mL)      | −0.0019 | 0.083 | −0.237 | 0.062 | −0.330 | 0.670 | −0.271 | 0.095 | 0.191 | 0.103 |
| TSH (uIU/mL)     | 0.068 | 0.368 | 0.122 | 0.337 | 0.974 | 0.206 | −0.110 | 0.516 | 0.028 | 0.812 |
| FSH (mIU/mL)     | −0.079 | 0.296 | −0.200 | 0.115 | 0.192 | 0.808 | 0.181 | 0.284 | −0.058 | 0.634 |
| LH (mIU/mL)      | 0.152 | 0.048 | −0.053 | 0.772 | 0.426 | 0.574 | 0.246 | 0.142 | 0.249 | 0.040 |
| E2 (pg/mL)       | 0.039 | 0.674 | −0.043 | 0.772 | −0.862 | 0.338 | 0.142 | 0.517 | 0.139 | 0.362 |
| Free T (pg/mL)   | 0.087 | 0.328 | 0.121 | 0.364 | 0.990 | 0.090 | −0.098 | 0.600 | −0.116 | 0.494 |
| Total T (pg/mL)  | 0.137 | 0.127 | 0.240 | 0.070 | −0.876 | 0.320 | 0.033 | 0.865 | −0.084 | 0.626 |
| DHEA-S (ug/mL)   | 0.056 | 0.524 | 0.044 | 0.743 | −0.057 | 0.943 | 0.086 | 0.646 | −0.205 | 0.210 |
| HbA1c (%)        | 0.010 | 0.922 | 0.061 | 0.703 | 0.998 | 0.039 | −0.055 | 0.785 | −0.058 | 0.754 |
| 17-OHP (ng/mL)   | 0.142 | 0.094 | −0.027 | 0.835 | −0.805 | 0.195 | 0.172 | 0.331 | 0.278 | 0.071 |
| BW (kg)          | −0.184 | 0.012 | −0.076 | 0.545 | 0.127 | 0.873 | −0.261 | 0.108 | −0.291 | 0.011 |
| HT (m²)          | −0.035 | 0.632 | −0.003 | 0.983 | −0.174 | 0.826 | −0.174 | 0.288 | −0.072 | 0.535 |
| BMI (kg/m²)      | −0.182 | 0.013 | −0.066 | 0.598 | 0.119 | 0.881 | −0.225 | 0.168 | −0.289 | 0.011 |

HA, hyperandrogenism; IM, irregular menstruation; PCO, polycystic ovaries; PRL, prolactin; TSH, thyroid stimulating hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol; T, testosterone; DHEA-S, dehydroepiandrosterone-sulfate; 17-OHP, 17-alpha-hydroxyprogesterone; BW, body weight; HT, height; BMI, body mass index.

with the higher value in those with hyperandrogenism and rather lowest value in IM + PCO group. Turhan et al. [16] have reported a significant, positive correlation between the ovarian volume and serum LH, testosterone, androstenedione and DHEA-S level in PCOS patients [5]. Also, Waki-moto et al. [17] have compared the precise ovarian volume obtained after unilateral ovariectomy with serum concentrations of testosterone, and they have concluded that the precise ovarian volume reflects ovarian activity measured as circulating concentration of AMH and testosterone as well as the LH/FSH ratio. However, Nardo et al. [18] have reported that the ovarian volume does not correlate with serum testosterone. In Nardo’s study, they measured ovarian volume using 3-dimensional ultrasound unlike other studies.

Regarding the serum level of DHEA-S, one of endogenous androgens, previous reports have been controversial. Christodoulaki et al. [19] have reported negative association of DHEA-S with ovarian volume in PCOS patients, while Turhan et al. [16] have reported rather positive correlation. Studies on Korean PCOS patients, including the previous literature and the current study, showed no statistically significant relation [10]. This might have been due to the difference of basic anthropometrics, as serum DHEA-S could be largely affected by BMI [20]. In Christodoulaki’s study, the average BMI was 25.7 ± 6.8, but in the current study, it was 22.54 ± 4.57. In addition, such varying results of the association between DHEA-S and ovarian volume could have been due to ethnic difference. Lasley et al. [21] reported that DHEA-S concentrations were the
highest, on average, among Chinese and Japanese and the lowest among African Americans and Hispanics. Further systemic reviews and meta-analysis at the intercontinental level would be required to clarify such less-explored association between DHEA-S and ovarian volume in various ethnicities.

Similarly, considering serum AMH level, no statistical significance in the relationship between ovarian volume and AMH was observed in the current study. Chun et al. [22] have also suggested that there is no relation between the two but instead positive correlation between total follicle count and AMH. According to the study of Han et al. [10], AMH is correlated with both ovarian volume and follicular number, follicle number seems more important than the ovarian volume. AMH is expressed in human follicles from the primary follicular stage toward the antral stage, immediately after recruiting right up to the selection stage, with the diameter of 4-6 mm [23]. Accordingly, the serum level of AMH runs proportional to the number of developing antral follicles in the ovaries [24]. As follicle number increases, the measurements of ovarian volume increases, so the follicle number becomes the more important factor in PCOS. In order to clarify the correlation between ovarian volume and AMH, studies with precise measurement of regarding entities and consequent statistical analysis corrected to the patient’s ovary volume and/or follicle number are warranted.

Other metabolic parameters crucial to PCOS include insulin resistance. Reid et al. [9] and Vila et al. [25] have reported that the ovarian volume is significantly related to insulin resistance. Nonetheless, the current study did not observe statistical significant relation between the patient’s ovarian volume and insulin level. This can also be attributed to the characteristics differences of the included patients; in the current study, the patient’s mean BMI was 22.54, while in the studies of Reid et al. [9] and Vila et al. [25] they were 25.7 and 28.42–30.33, respectively. PCOS does have important physiologic relations to insulin resistance; among Korean patients with PCOS, however, obesity seems rare, and associated metabolic risks, such as insulin resistance, seems infrequent and has different modality from that of western neighbors [4].

Other than the actual parameters associated with PCOS, measurement modalities and their interpretation could have been exerted on understanding the results of the current study. One issue related to ovarian volume is the threshold of the ovarian volume and follicle number to define PCOM according to the age group. Kim et al. [26] have suggested that the ovarian volume decreases gradually with aging and that the threshold to define PCOM should be lowered starting at age 30. Further studies considering age-related changes of ovarian volume and follicle number are needed to clarify this issue.

When further exploring the relationships between parameters of PCOS, BMI had negative correlation with AMH in the current study. Jaswa et al. [27] have concluded that BMI appears to influence the reduction in serum AMH levels, as observed in women with increasing body size. Moreover, Moslehi et al. [28] have suggested that there is negative correlation between BMI and AMH in reproductive aged women older than 35 years, with obese women having significantly lower AMH levels compared to their non-obese counterparts. In the current study, BMI was rather homogenous across the subgroups, without statistically significant different. Interestingly, body weight and BMI were still negatively correlated with AMH in the overall patient group and IM-PCO group in subgroup analysis; in patients with HA characteristics, such tendency of data was not observed.

The critical limitation of the current study is that the number of patients included in this study was relatively small; multicentered studies with the larger cohort are evidently warranted. Nevertheless, the study population is homogenous, all with Korean ethnicity. Furthermore, their clinical management and ultrasonographic evaluation were performed by a single physician, which could offset possible unpredicted variables that could have affected the results of the study. Especially, all ultrasonographic measurements of the ovarian volume were performed by a single professional gynecologist specialized in reproductive endocrinology and gynecologic ultrasonography in order to reduce such unintended measurement errors; follicle number measurements included follicle counts throughout the entire ovary, and ovarian volume measurements adopted the simplified formula of 0.5 × longitudinal length × anteroposterior width × transverse thickness, as previously described [29,30].

8. Conclusions

In conclusion, the current study evaluated the association of ovarian volume with clinical and laboratory parameters of Korean PCOS patients, and according to the results, the ovarian volume, quantified by ultrasonographic measurements, was significantly related to the increasing serum levels of free testosterone, total testosterone and 17-OHP in such Korean PCOS patients. Further studies with larger population considering age-related changes of ovarian volume and follicle number along with metabolic parameters are required to clarify this important influence of ovarian volume on the patient’ metabolic parameters, as it could guide not only the clinicians to provide the patients with more efficient, patient-specific therapeutic strategies but also the researchers to better explore the underlying pathophysiological pathway of PCOS embracing critical metabolic aspects of the disease.

Author contributions

SL and JJ designed the research study. SL performed the research. EY provided help and advice on data gathering and analysis. SL and HL analyzed the data. SL, HL and
JJ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was waived from ethics approval by the institute review board of Pusan National University Hospital due to its retrospective observational character using analysis of previously-recorded patient medical chart without any information allowing personal identification.

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Conflict of interest
The authors declare no conflict of interest.

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