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Original Article

Accuracy of anti-Müllerian hormone and total follicles count to diagnose polycystic ovary syndrome in reproductive women

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ABSTRACT

Objective: Recently, there was a new recommendation of ultrasonographic criteria to diagnosis polycystic ovary syndrome (PCOS). In addition, serum anti-Müllerian hormone (AMH) was proposed as a surrogate marker for diagnosis of PCOS, but AMH cut-off level for diagnosis of PCOS is unclear. This study aimed to investigate the accuracy of serum AMH and evaluate new ultrasonographic criteria, follicle number per ovary (FNPO) threshold ≥ 25 follicles and ovarian volume (OV) > 10 mL, for diagnosis of PCOS.

Materials and methods: A cross-sectional study was conducted. Fifty-five PCOS women and sixty-three normal ovulatory, non-hyperandrogenic women were recruited. Transvaginal or transrectal ultrasonography was performed in all participants to evaluate follicle number and OV. Serum AMH was evaluated in both study groups.

Results: The mean age of the participants was 25.1 ± 5.3 years old in PCOS group and 29.7 ± 7.2 years old in control group. Mean AMH, FNPO and OV in PCOS women were significantly higher than those in non-PCOS women. The area under the receiver-operating characteristic (ROC) curve of AMH was 0.903. The threshold of AMH at 4.7 ng/mL offered the best compromise between 80% sensitivity and 77.8% specificity. The appropriated threshold values for FNPO, follicle number per cross-section (FNPS) and OV were 15 follicles, 7 follicles and 6.5 mL, respectively. Serum AMH level was significantly positively correlated with FNPO, FNPS and OV in both PCOS and control groups. In PCOS women, serum AMH showed strongly correlation with FNPO ($r = 0.53$, $p < 0.001$) and weakly correlation with total testosterone ($r = 0.283$, $p = 0.036$).

Conclusion: Serum AMH had a good diagnostic performance for diagnosis of PCOS presenting with oligo/anovulation and hyperandrogenism. AMH threshold at 4.7 ng/mL was the best compromise level for diagnosis of PCOS. FNPO ≥15, FNPS ≥7 and OV ≥ 6.5 mL were reliable threshold for detecting polycystic ovaries in women with frank manifestation of PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder, affecting 10% of reproductive-aged women [1]. This syndrome is associated with many long term health problems such as central obesity, metabolic syndrome, insulin resistance and diabetes mellitus [2–4]. Therefore, making diagnosis of PCOS is essential because women could be benefit from early detection of associated conditions, planning therapeutic strategies in an affected subject and prevention long term medical problems.

The diagnosis of PCOS is based on the 2003 Revised Rotterdam criteria. Ultrasonographic evidence of polycystic ovarian morphology (PCOM) which is defined as the presence of ≥12 follicles measuring 2–9 mm in diameter and/or ovarian volume (OV) > 10 mL in at least one ovary is one of the criteria [5]. However, the evidence after consensus statement of the Rotterdam criteria showed that the definition of PCOM was inappropriate. According to advancement of ultrasound technology, PCOM is frequently found in both PCOS

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women and non-PCOS women [6,7]. Previous studies reported different follicle number per ovary (FNPO) threshold to discriminate between non-PCOS and PCOS women [8,9]. In 2014, a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society recommends FNPO ≥25 follicles as a new threshold for the definition of PCOM [10]. Nevertheless, ultrasonography still has many limitations, such as observer variability and ultrasound technology.

Apart from using ultrasonographic criteria, serum anti-Müllerian hormone (AMH) was proposed as a surrogate marker for diagnosis of PCOS [11]. The AMH is a glycoprotein produced by the granulosa cells of preantral and antral follicles. Serum AMH concentrations increase in PCOS and significantly correspond to increase in follicle number in PCOS [11]. The previous studies showed good accuracy of AMH for PCOS diagnosis, but the cutoff value of AMH were different among studies [8,11]. The meta-analysis of AMH in diagnosing symptomatic PCOS women demonstrated 79.4% specificity and 82.8% sensitivity at cutoff value of 4.7 ng/mL [12].

The aim of the present study was to investigate the accuracy of AMH for diagnosis of PCOS. The secondary objective was to evaluate new ultrasonographic criteria of PCOM by FNPO threshold ≥25 follicles and ovarian volume >10 mL for diagnosis of PCOS in reproductive PCOS women.

Materials and methods

The cross-sectional study was conducted between April 2016 and March 2017 at Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University. Ethical approval was obtained from Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University with certificate of approval (COA) number Si 229/2016. All participants were informed and written consent to participate in this study.

This study had 2 population groups: PCOS and control group. The PCOS participants were women 18–45 years of age, who diagnosed with PCOS by the Revised Rotterdam Criteria 2003 as having both 1) oligo-anovulation and 2) clinical and/or biochemical signs of hyperandrogenism, were enrolled in the study. Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid disease or hyperprolactinemia were assessed before diagnosis of PCOS. Oligo-anovulation was defined as menstrual interval longer than 35 days. Clinical hyperandrogenism was defined as presence of acne, hirsutism or androgenic alopecia. Acne was assessed by using the recommended criteria from Dermatological Society of Thailand in 2011 [13]. Severity of acne was graded as three levels. Mild acne was defined as presence of comedone and/or <10 papules or pustules. Moderate acne was presented as > 10 papules or pustules and/or <5 nodules. Severe acne was shown as numerous of papules or pustules or nodules. Hirsutism was evaluated by using the modified Ferriman-Gallwey scoring system (mFG), cut-off score ≥ 5 indicated hirsutism. This cut-off score was used because mFG score of 5–6 was appropriated to define hirsutism in the studies including East Asian population [14–17]. Androgenic alopecia was evaluated using Ludwig scale. Biochemical hyperandrogenemia was defined as serum total testosterone level greater than 0.8 ng/mL [18]. The control participants were healthy women aged 18–45 years old. They had to have regular menstrual cycle with interval of 21–35 days and no clinical and biochemical hyperandrogenism. The participants in both PCOS and control groups were ineligible if they had used steroid drug or hormone during the 3 months prior to enrollment and had previous history of ovarian surgery.

All participants were asked about general gynecologic history and their menstruation. They were received physical examination and evaluated signs of hyperandrogenism. Then all participants were scanned pelvic ultrasonography and taken venous blood puncture.

Ultrasonography measurements

Transvaginal or transrectal ultrasonography (TVS or TRS) was performed by one of two examiners to evaluate follicle number and ovarian volume. Control subjects were evaluated in the early follicular phase between days 2^{nd}–5^{th} of menstrual period. Women with PCOS were evaluated at anovulatory or follicular phase. Ultrasonography measurements followed the protocol as mention in literature [10,19], using an Aloga Alpha 6 with 8 MHz transvaginal transducer. Ultrasonography measurements were taken in real-time. Both ovaries were scanned from inner to outer margin in the longitudinal plane. The participant was excluded if there was a dominant follicle (≥10 mm), corpus luteum or other abnormal ovarian mass. In case of suspicious evidence of ovulation at the time of ultrasound performing, the participant was also excluded from the study. After determination of the longest axis of the ovary, the length and thickness were measured and the OV was calculated by using the formula for a prolate ellipsoid (0.5 × length × width × thickness). Follicle size was expressed as the mean of two perpendicular measurements and follicles between 2 and 9 mm were counted. For each ovary, follicle number per cross-section (FNPS) were counted in the plane of the ovary that contained maximum follicles and FNPO were counted by slow and continuous scanning of the entire ovary, from one margin to the other. The ovarian parameters were recorded from both ovaries in each participant and greater values of FNPO, FNPS, OV in each participant were used for analysis.

Reliability analysis

The participants in both PCOS group and control group were randomly selected and simultaneously evaluated by two sonographers to assess the reliability for counting FNPO and FNPS. Based on an intra-class correlation coefficient analysis from previous study, the level of inter-observer agreement for FNPO and FNPS was 0.84 and 0.94, respectively [9]. In this study, inter-observer reliability was 0.959 for FNPO and 0.945 for FNPS. Intra-observer reliability of the first operator was 0.986 and the second operator was 0.981.

Biochemical assays

In PCOS group, blood was taken in the morning at the same day of TVS or TRS performing. Hormonal assays included serum total testosterone and AMH were evaluated in both PCOS and control group. Serum assays were performed in the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital. Serum total testosterone was measured by electrochemiluminescence immunoassay (ECLIA) using Cobas8000 c602 (Roche Diagnostic, Germany) with intra-assay coefficient of variation (CV) of 1.57%–2.26% and inter-assay CV of 2.92%–4.32%.

For serum AMH measurement, blood samples were centrifuged at room temperature within 30 min. Serum was stored at −80 °C until AMH analysis. Serum AMH was assayed by Elecsys AMH ECLIA on a Cobas e602 automated assay system (Roche Diagnostic, Germany) with intra-assay CV of 0.55%–0.86% and inter-assay CV of 0.93%–1.02%. The available range of measurement using the Elecsys AMH assay is between 0.03 and 23 ng/mL.

Sample size

The sample size was calculated based on the meta-analysis study of Iliodromiti S et al., in 2013 [12]. Serum AMH at cutoff