Review

Anti-Müllerian hormone levels in the diagnosis of adolescent polycystic ovarian syndrome: a systematic review and meta-analysis

Yumiko Tsukui1), Yoshikazu Kitahara1), Yuko Hasegawa1), Mio Kobayashi1), Satoko Osuka2) and Akira Iwase1)

1) Department of Obstetrics and Gynecology, Gunma University Graduate School of Medicine, Maebashi 371-8511, Japan
2) Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan

Abstract. Polycystic ovary syndrome (PCOS) is an endocrine disorder that causes menstrual cycle irregularities and infertility. PCOS is diagnosed based on hyperandrogenism, polycystic ovarian morphology (PCOM), and an-/oligo-ovulation. Upregulation of anti-Müllerian hormone (AMH) in the serum of women with PCOS may be another suitable alternative diagnostic criterion for PCOM. However, previous meta-analyses have reported conflicting results due to the age-dependent decline in serum AMH levels. Therefore, we performed a meta-analysis to evaluate the threshold of AMH for the diagnosis of PCOS in adolescents and women in their early twenties. Fifteen trials were included in this meta-analysis. PCOS is diagnosed with either Rotterdam criteria, NIH, or AE-PCOS. AMH levels were significantly higher in adolescents with PCOS (weighted mean difference, 3.05; 95% confidence interval: 2.09–4.01) than in the control group. The cutoff values of AMH for the diagnosis of adolescent PCOS were 6.1, 6.26, 7.03, 7.11, 7.2, and 7.25 ng/mL in the studies that reported the usefulness of AMH levels. The summary receiver operating characteristic analysis of the diagnostic accuracy demonstrated that the specificity and sensitivity were 81% and 66.3%, respectively. Our meta-analysis demonstrates that AMH may be a useful diagnostic test for adolescent PCOS and, based on the previous studies included in the meta-analysis, its cutoff value was estimated to be 6–7 ng/mL.

Key words: Adolescent, Anti-Müllerian hormone (AMH), Ovarian reserve, Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that occurs in approximately 5–20% of women of reproductive age [1, 2]. PCOS can also cause menstrual irregularities and infertility [3]. Other complications of PCOS include hyperandrogenism, polycystic changes in the ovaries, an-/oligo-ovulation, insulin resistance, and obesity [4]. PCOS is a concerning disease from the perspective of preventive medicine, as it may increase the risk of metabolic syndrome [5-8] and endometrial cancer [9, 10]. PCOS encompasses a heterogeneous group of diseases with a wide variety of symptoms, and there are several diagnostic criteria for this condition. In 1990, the conference on PCOS sponsored by the National Institutes of Health (NIH) proposed the diagnostic criteria in which PCOS is defined as unexplained hyperandrogenic an-/oligo-ovulation (NIH criteria) [11]. In Europe, the Rotterdam Criteria (2003) are widely used for the diagnosis of PCOS. Under these criteria, at least two of the following three criteria must be met: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenemia, and polycystic ovarian morphology (PCOM) [12]. Two years later, the Androgen Excess Society issued the diagnostic criteria that included hyperandrogenemia as an essential condition for PCOS (AE-PCOS) [13].

In adolescent females, the ovaries begin to secrete sex steroids, and many patients with PCOS begin to show symptoms (i.e., adolescent PCOS). Although there is no clear definition of PCOS in adolescents, it has been reported that the same diagnostic criteria can be applied to adults [14, 15]. A recent meta-analysis revealed a possible risk of metabolic syndrome in adolescent PCOS, even when controlling for obesity [16]. Even in healthy adolescents, many signs of PCOS are common, including
irregular menstruation, hypertrichosis, acne, and PCOM [17, 18]. Therefore, the differential diagnosis between PCOS and non-PCOS patients, who have similar symptoms, remains challenging. PCOM may also occur in healthy females. PCOM may not be helpful in diagnosing PCOS in adolescents, as the frequency of PCOM has been reported to be particularly high in the first 8 years after menarche [19]. Another problem is that transvaginal ultrasonography is difficult to perform in adolescents; therefore, transabdominal ultrasonography is often performed. It is difficult to visualize the ovaries using transabdominal ultrasonography, and PCOM signs may not be accurately assessed.

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein encoded by a gene on chromosome 19 and belongs to the transforming growth factor-β superfamily [4, 20]. In women, it is secreted by the granulosa cells of preantral and small antral follicles and is reported to be involved in the development of primordial to primary and mature follicles. AMH has been used as a marker of ovarian reserve. The antral follicle count (AFC) was also measured as a marker of ovarian reserve. AMH and AFC are often used to predict responsiveness to ovulation induction [21], predict menopause [22], and diagnose premature ovarian insufficiency [23]. Serum AMH concentrations reflect the ovarian follicle pool and are strongly dependent on the number of preantral and small antral follicles in the early follicular phase of the menstrual cycle [24, 25].

As the secretion of AMH increases with the number of preantral and small antral follicles, women with PCOS have significantly higher serum AMH levels, irrespective of age. Therefore, AMH has proven useful as a marker for PCOS and as an alternative to AFC for PCOS diagnosis [4, 26]. To date, several studies have focused on AMH as a diagnostic marker for PCOS at all ages, mainly in adulthood [3, 4]. Although these studies have recommended various AMH cutoff values, the sensitivity and specificity of AMH for the detection of PCOS are inconclusive [27-29]. Whether thresholds should be age-specific is also debated [3] because, in normal populations, AMH levels change significantly during reproductive years.

The purpose of this systematic review was to evaluate the threshold of AMH for the diagnosis of PCOS in adolescents and women in their early twenties. PCOS evaluation using AMH levels may be useful because, as previously mentioned, it is difficult to evaluate PCOM using ultrasonography, especially in adolescents, and because PCOM is also found in healthy women. In addition, if all ages are included it would be difficult to set a cutoff value for AMH. This is because AMH gradually declines over the age of 25 years [30]. Therefore, in adolescents and women in their early twenties, AMH values exhibit limited fluctuations [30]. Therefore, in the present study, we conducted a meta-analysis restricted to adolescents and women in their early twenties to evaluate the usefulness of AMH levels in PCOS diagnosis.

Materials and Methods

Literature search and study selection

We conducted a systematic literature review in PubMed, Web of Science, and Science Direct to identify relevant studies published up to August 2021. The search was limited to human studies published in English, and the following search terms were applied: PCOS or “polycystic ovary syndrome,” adolescent or adolescence, and AMH or AFC. In addition, the reference lists of relevant publications were manually searched to include further relevant studies.

We included studies that met the following criteria: 1) assessed serum AMH or AFC and 2) included adolescent women diagnosed with PCOS (age range, up to 29 years). All prospective, retrospective, cross-sectional, and case-report studies were included in this review. Studies were excluded for the following reasons: 1) published as a table of contents, indexes, reviews, meta-analyses, or textbooks, and 2) measured AMH in patients with PCOS but did not compare the levels with those of the controls.

Data extraction and comparison

The following data were extracted from the included articles: first author, year of publication, study design, PCOS diagnosis method, patient characteristics (age and body mass index), AMH level, and AFC. The corresponding author was contacted if necessary. AMH levels were compared between the PCOS and control groups. AFC was also compared between the PCOS and control groups. The results were expressed as weighted mean differences.

Statistical analysis and hierarchical summary

receiver operating characteristic (HSROC)

The data were pooled using the RevMan software (Review Manager, version 5.4; Cochrane Collaboration). The mean and standard deviation (SD) of the AMH values were extracted from the articles. The AMH values were converted to ng/mL by dividing these by 7.14 when they were described in pmol/L. The weighted mean differences in the AMH values between cases and controls were calculated. Heterogeneity among studies was assessed based on the results of F statistics. A random-effects model was used for the meta-analysis. Statistical significance was set at p < .05.
We used MetaDTA (Diagnostic Test Accuracy Meta-Analysis, version 2.01; Freeman) [31] to calculate HSROC parameters. The HSROC curve, pooled sensitivity, and specificity were obtained using the HSROC parameters in MetaDTA.

**Results**

**Literature search**

A literature search was conducted in the databases, and 380 articles were obtained. Duplicate and irrelevant studies were excluded, and 102 full-text articles were screened. Eighty-three articles were excluded for the following reasons: review or protocol articles, lack of actual data, duplication, use of other surgical methods, animal experiments, and inappropriate controls. Finally, 19 full-text studies were included in this systematic review (Fig. 1).

**Characteristics of the included studies**

A summary of the studies included in this systematic review is shown in Table 1. These included four prospective studies [32-35], one retrospective study [36], six case-control studies [37-42], and eight cross-sectional studies [43-50]. In terms of PCOS diagnostic criteria, 16 studies used the Rotterdam criteria, four used NIH criteria (one used both criteria), and one used AE-PCOS. Nine articles excluded cases within two years of menarche, and one article excluded cases within one year of menarche. Four of the 19 eligible studies were excluded from the meta-analysis because of a lack of information on AMH measurement means and/or SDs [33, 43, 48, 50] (Table 2).

**Meta-analysis for AMH and AFC**

We evaluated the differences in AMH levels between adolescents, including women in their early twenties, diagnosed with PCOS, and control women. AMH levels tended to be higher in women with PCOS, with a weighted mean difference of 3.05 (95% confidence interval [CI]: 2.09–4.01; $I^2$: 79%; Fig. 2A) than in control women. The meta-analysis recruited 7 studies that excluded adolescents <1 or 2 years from menarche also exhibited significantly higher AMH levels in adolescent PCOS (mean difference 2.91; 95% CI: 0.74–5.09; $I^2$, 87%). This exclusion avoids the potential for false-positive diagnoses. We also analyzed the differences in AFC between adolescent women diagnosed with PCOS and control women. AFC also tended to be higher in women with PCOS, with a mean difference of 7.14 (95% CI: 2.70–11.59; $I^2$, 98%; Fig. 2B).

**HSROC**

The HSROC curve is represented in Fig. 3A with each study point and a summary estimate. The 95% confidence and 95% predictive regions are also shown. The specificity and sensitivity in the HSROC are 0.81 (95% CI: 0.749–0.81) and 0.663 (95% CI: 0.572–0.744), respectively. The sensitivity and specificity of the individual studies are shown in forest plots (Fig. 3B and C, respectively).

**Discussion**

We compared the differences in AMH levels between adolescent/early-twenties women with PCOS and healthy controls. AMH levels were significantly higher in PCOS individuals than in the age-matched controls, with an approximate difference of 3.05 ng/mL. Based on the AUC value of the summary ROC, we considered that AMH might be useful in diagnosing adolescent PCOS.

Several studies have reported the usefulness of AMH for diagnosing PCOS in various age groups. In one meta-analysis, a cutoff of 4.7 ng/mL was suggested [18]. However, subsequent guidelines stated that the cutoff for AMH varies widely between reports and cannot be used to diagnose PCOS [19]. One reason for this variability is that AMH gradually decreases after the age of 25 years.
Table 1  Studies included in the systematic review

| Author, Year     | Study design | Criteria of PCOS | Inclusion: Age (y) | Exclusion | PCOS | Control |
|------------------|--------------|------------------|-------------------|-----------|------|---------|
|                  |              |                  |                   | n         | Age (y), mean ± SD or median (range) or [IQR] | BMI, mean ± SD or median (range) or [IQR] | n         | Age (y), mean ± SD or median (range) or [IQR] | BMI, mean ± SD or median (range) or [IQR] |
| Asanidze, 2019   | Prospective  | Rotterdam        | 13–19             | <2y from menarche | 90   | 17.8 ± 3.4 NS | 20 | 17.2 ± 3.9 NS |
| Cengiz, 2014 (half) | Prospective | Rotterdam        | NS                | <2y from menarche | 29   | 18.2 ± 1.85 20.1 ± 2.61 | 28 | 18.3 ± 1.21 21.4 ± 2.94 | normal-weight subgroup |
|                  | Prospective  | Rotterdam        | NS                | <2y from menarche | 29   | 17.8 ± 1.74 28.3 ± 3.46 | ↑ | ↑ | overweight subgroup |
| Hart, 2010       | Prospective  | Rotterdam        | NS                | <2y from menarche | 64   | 15.2 ± 0.45 24.43 ± 5.12 | 149 | 15.4 ± 0.56 22.07 ± 2.94 |
| Hou, 2016        | Case control | Rotterdam, NIH   | 12–18             | <2y from menarche | 14   | 14.9 ± 1.87 28.9 ± 4.86 | 10 | 15.4 ± 1.90 22.6 ± 5.06 |
| Khashchenko, 2020 | Cross-sectional | Rotterdam | NS                | <2y from menarche | 130  | 16 [15–17] 22.4 [19.9–27.2] | 30 | 16 [15–17] 20.2 [18.4–21.8] |
| Kim, 2017        | Cross-sectional | NIH             | 10–20             | <2y from menarche | 46   | 14.9 ± 1.36 37.7 ± 7.46 | 43 | 14.4 ± 1.31 33.1 ± 7.21 | obese PCOS |
| Kocaay, 2018     | Cross-sectional | Rotterdam | 14.3–17.2         | <2y from menarche | 29   | 15.55 ± 1.33 NS | 55 | 15.4 ± 1.45 NS |
| Li, 2010         | Case control  | Rotterdam        | 17–25             | <2y from menarche | 47   | 20.30 ± 2.73 21.25 ± 4.29 | 40 | 21.05 ± 3.05 20.04 ± 1.83 |
| Merino, 2017     | Cross-sectional | Rotterdam | 11.4–19.8         | <2y from menarche | 35   | 15.9 ± 1.9 22.6 ± 2.5 | 67 | 15.3 ± 2.7 22.9 ± 2.9 |
| Park, 2010       | Prospective   | NIH              | NS                | <2y from menarche | 153  | 15.7 ± 1.24 34.1 ± 7.42 | 39 | 14.6 ± 2.50 29.9 ± 6.24 |
| Paweleczak, 2012 | Case control  | Rotterdam        | 12.3–17.7         | <2y from menarche | 23   | 15.2 ± 1.84 NS | 12 | 14.08 ± 1.7 NS |
| Savas-Erdeve, 2016 | Cross-sectional | Rotterdam | NS                | <2y from menarche | 21   | 15.7 ± 1.58 24.06 ± 7.0 | 30 | 16.0 ± 1.84 24.1 ± 8.84 |
| Simpson, 2020    | Cross-sectional | Rotterdam | 12–20             | <2y from menarche | 52   | 16.1 ± 1.8 31.9 ± 8.1 | 23 | 15.7 ± 1.4 32.6 ± 11.1 |
| Sophor, 2014     | Case control  | NIH              | 13–21             | <2y from menarche | 15   | 16.6 ± 2.1 NS | 16 | 18.6 ± 2.6 NS |
| Tokmak, 2015     | Case control  | Rotterdam        | 15–23             | <2y from menarche | 43   | 18.9 ± 2.2 22.9 ± 4.7 | 47 | 18.4 ± 2.4 21.8 ± 2.8 |
| Tokmak, 2016     | Case control  | Rotterdam        | 15–21             | <2y from menarche | 27   | 18.5 ± 2.4 22.3 ± 1.95 | 32 | 18.0 ± 2.3 20.1 ± 3.0 | with insulin-resistance |
| Villamoel, 2015  | Cross-sectional | Rotterdam | <=20              | <1y from menarche | 26   | 17.3 ± 1.9 NS | 63 | 16.6 ± 1.5 NS |
| Wright, 2015     | Retrospective | AE-PCOS          | NS                | <2y from menarche | 35   | 21 (16-29) NS | 14 | 21 (16-29) NS |
| Yetim, 2016      | Cross-sectional | Rotterdam | 14.5–20           | <2y from menarche | 53   | 16.72 ± 1.41 NS | 26 | 15.18 ± 2.0 NS |

NS, not specified; IQR, interquartile range
making it difficult to present a fixed AMH value as a cutoff. However, when limited to adolescents and women in their early twenties, AMH fluctuates relatively little, so it may be easier to establish a fixed cutoff value. In previous studies, the cutoff values of AMH for the diagnosis of PCOS in adolescents were reported as 6.1, 6.26, 7.03, 7.11, 7.2, and 7.25 ng/mL (Table 3), suggesting that a suitable cutoff value for PCOS in adolescents and women in their early twenties, might be 6–7 ng/mL. This was higher than the 4.7 ng/mL found in the meta-analysis for all ages. Although there has been an ongoing debate as to whether AMH, similar to PCOM, should be included as one of the diagnostic criteria for PCOS, the range of serum AMH cutoff values can be narrowed down when considering adolescent PCOS alone.

We included five studies for the meta-analysis to evaluate the difference in AFC between adolescents with PCOS and controls. The Rotterdam criteria were used in all of the adopted studies. PCOM is one of the three Rotterdam diagnostic criteria. Therefore, a significant increase in AFC is expected in adolescent PCOS patients. The same five studies were also included in the meta-analysis for AMH. Therefore, we can say that AMH and AFC are both elevated in adolescent PCOS.

### Table 2  Studies not included in the meta-analysis

| Author, Year | AMH (ng/mL) | AFC |
|--------------|-------------|-----|
| Cengiz, 2014 (normal-weight) | 8.7 (4.66) | 6.5 (6.96) |
| Cengiz, 2014 (overweight) | 7.2 (6.83) | 10.0 (10.25) |
| Khashchenko, 2020 | 9.5 [7.5–14.9] | 5.8 [3.8–6.9] |
| Simpson, 2020 | 6.7 (0.5–14.4) | 3.6 (1.4–9.6) |
| Yetim, 2016 | 11.02 (1.66–50.6) | 4.06 (0.93–11.96) |

1 median (range); 1 median [interquartile range]; * comparison of 3 groups.

![Fig. 2](https://example.com/figure2.png)

Fig. 2  Forest plot comparing the anti-Müllerian hormone (AMH) (A) and antral follicle count (AFC) (B) between adolescent polycystic ovary syndrome (PCOS) and control.
Imaging evaluation (especially transvaginal ultrasonography) is effective for the evaluation of polycystic ovaries. However, transvaginal ultrasonography is often difficult to perform in adolescent women who have never had sexual intercourse. In such cases, transabdominal ultrasonography or magnetic resonance imaging (MRI) can be performed. It may be difficult to observe the ovaries using transabdominal ultrasonography. MRI is effective in visualizing the ovaries and has been reported to show follicles more clearly [51]. However, some reports suggest that the number of follicles depicted varies depending on slice thickness [52] and that the number of

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**Fig. 3** Hierarchical summary receiver operating characteristic (HSROC) analysis with summary estimate, 95% confidence region, and 95% predicted region (A). Forest plot of sensitivity (B) and specificity (C) of all included studies in the HSROC analysis.

**Table 3** Studies included in the diagnostic test accuracy meta-analysis

| Author, Year          | ROC (AMH) | Sensitivity | Specificity | AUC [95%CI]        | Cut-off (ng/mL) | p       |
|-----------------------|-----------|-------------|-------------|--------------------|-----------------|---------|
| Sopher, 2014          |           | 40          | 93.8        | NS                 | 3.4             | NS      |
| Yetim, 2016           |           | 81.1        | 92.3        | 0.88 [0.80–0.96]   | 6.1             | <0.001  |
| Kim, 2017             |           | 67          | 81          | 0.788 [0.687–0.868] | 6.26            | <0.0001 |
| Merino, 2017          |           | 58.8        | 82.1        | 0.758              | 7.03            | 0.0001  |
| Tokmak, 2016          |           | 84          | 66.7        | 0.763 [0.607–0.920] | 7.11            | 0.004   |
| Khashchenko, 2020     |           | 76          | 89          | 0.869              | 7.2             | <0.05   |
| Savas-Erdeve, 2016    |           | 58.5        | 83.3        | 0.700 [0.591–0.808] | 7.25            | 0.001   |
| Li, 2010              |           | 61.7        | 70          | 0.664 [0.551–0.778] | 8               | NS      |
| Tokmak, 2015          |           | 48.8        | 77.1        | 0.579 [0.435–0.705] | 14              | 0.198   |

NS, not specified.
AMH in adolescent PCOS diagnosis

Follicles may not be assessed due to a relatively high chance of imaging artifacts [53]. Another disadvantage is the higher cost of MRI compared to ultrasound. Therefore, AMH can be considered a more objective evaluation standard.

PCOS-related health risks have been reported over several decades. A recent meta-analysis revealed the possible risk of increased blood pressure and dysregulation of lipid metabolism in adolescent PCOS, even after controlling for obesity [16]. Atypical endometrial hyperplasia (AEH)/endometrial cancer (EC) is another risk associated with PCOS. Okamura et al. reported that 11 of 14 PCOS women with AEH/EC under 35 years of age exhibited irregular menstruation and/or amenorrhea during adolescence. They also showed that hormonal therapy for AEH/CE with PCOS under 35 years of age was not as effective as that for AEH/EC without PCOS [54].

Taken together, early follow-up enables early diagnosis of metabolic syndromes and AEH/EC and consequently early intervention and/or specific hormonal treatments even for adolescent may reduce the future risk of metabolic syndromes and AEH/EC. Therefore, more objective diagnostic criteria for adolescent PCOS are needed.

A previous report indicated that high AMH levels in adolescence are risk factors for the development of PCOS in adulthood and beyond [55]. This study compared adolescent AMH levels in women with and without PCOS in adulthood and found that women with PCOS in adulthood predominantly had higher adolescent AMH levels. In addition, when the cutoff for AMH in adolescence was set at 6 ng/mL, the sensitivity and specificity for PCOS in adulthood were reported to be 50% and 87%, respectively. In this regard, it is meaningful to measure AMH in adolescence not only for the diagnosis of PCOS but also as a risk determinant in later life.

AMH is not only a biomarker for PCOS but also a molecule implicated in PCOS pathophysiology [25]. AMH plays a role in folliculogenesis by regulating the recruitment of primordial follicles and FSH-dependent follicle development [56]. Increased serum AMH levels may be involved in the disturbance of folliculogenesis in PCOS patients. Furthermore, aberrant production of AMH by granulosa cells has been reported in PCOS [57]. Therefore, excess biological and clinical AMH may play a significant role in the pathophysiology of adolescent PCOS.

The limitations of this study can be divided into two major categories. First, a summary ROC curve cannot produce a cutoff value similar to that of individual ROCs. Therefore, studies with pooled data or larger-scale studies are required to establish cutoff values. In addition, a uniform AMH kit may be required to establish a more accurate cutoff value, as there are multiple types of AMH measurement kits [58-61] and the data may be inconsistent. Second, physiological PCOM is more likely to occur during puberty, even in the absence of PCOS [62]. This may be because the hypothalamic-pituitary-ovarian regulatory system is immature during puberty and anovulatory cycles are common. Therefore, more than half of the studies included in this meta-analysis excluded adolescent girls with <1 or 2 years from menarche. Subgroup analyses of these studies showed similar results. We performed a meta-analysis to determine whether AMH levels are significantly higher in adolescent PCOS patients and useful as a PCOS diagnostic alternative to PCOM. However, physiological PCOM in adolescent girls should be discussed using existing diagnostic criteria. Several issues may arise from the broadness of the Rotterdam criteria. Therefore, strict evaluation using sub-group analysis that is specified with any two of three criteria (PCOM, hyperandrogenism, and an-/oligo-ovulation) would be needed.

AMH levels may be higher in physiological PCOM, but there are no reports examining whether AMH levels are as high as those in PCOS. Aberrantly upregulated production of AMH from granulosa cells has been reported in PCOS [57]. Therefore, increased AMH levels in adolescent PCOS patients can be distinguished from just a substitute for PCOM. One study reported that high AMH levels in adolescence are a risk factor for PCOS in adulthood and beyond [55]. Considering the aberrant function of granulosa cells, increased AMH should also be investigated in relation to PCOS pathophysiology.

In conclusion, our meta-analysis demonstrated that AMH may be useful in diagnosing PCOS in adolescents. Further investigation with larger prospective cohort studies is required to confirm the predictive significance of adolescent AMH levels for late-onset PCOS in adulthood.

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