# The role of anti-Müllerian hormone in diagnosing and managing PCOS

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Because multiple subjective factors can cloud the diagnosis of polycystic ovary syndrome, anti-Müllerian hormone (AMH) level, an objective value, has been studied as a potential supplement to polycystic ovarian morphology in diagnosing and managing the syndrome. The author reviews recent evidence demonstrating the role of AMH in this regard.

KEY WORDS: polycystic ovary syndrome, PCOS, anti-Müllerian hormone, AMH, hyperandrogenism, infertility
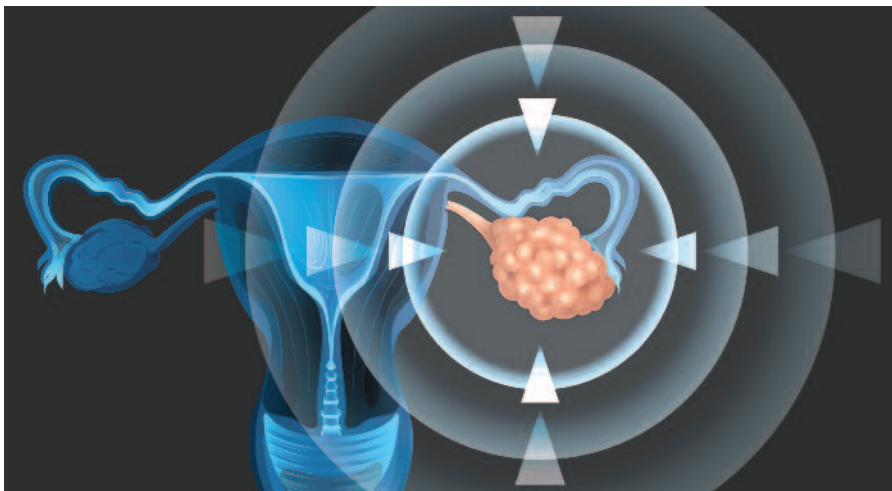
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting females of reproductive age and the leading cause of anovulatory infertility.[1] Lack of correct diagnosis and management of PCOS can lead to reproductive challenges (e.g., infertility, early miscarriage, gestational diabetes), metabolic disorders (e.g., type 2 diabetes mellitus), or cardiovascular disorders (e.g., hypertension, dyslipidemia).[2] Advanced practice nurses (APNs) are tasked with correctly diagnosing and managing PCOS in order to prevent these associated morbidities, which can compromise quality of life.

According to the Rotterdam criteria for diagnosing PCOS, at least two of these three elements must be met: clinical and/or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian (PCO) morphology.[3] PCO morphology has been defined as the presence of more than 12 follicles measuring <10 mm and/or an increased ovarian volume (>10 mL) without a cyst or dominant follicle in either ovary.[3] According to Lujan et al,[4] the inclusion of ultrasonographic (USG) evidence of polycystic ovaries as a diagnostic marker has substantially broadened the phenotypic spectrum of PCOS, yet much debate surrounds the validity of these newly identified milder variants of the syndrome.

In light of such concerns, the use of anti-Müllerian hormone (AMH) level as a more reliable marker for PCO morphology than follicle size and number on USG has been investigated in recent studies. Results of these studies indicate a consistent relationship between AMH level and USG estimates of antral follicle count (AFC) and ovarian volume.[5-7] Research has shown that serum AMH levels are significantly increased in women with PCOS versus those without PCOS.[1,5,6] Although further research is needed, serum AMH measurement may prove to be a useful tool for APNs in diagnosing phenotypes of PCOS that satisfy the Rotterdam criteria.

Development of polycystic ovaries

To appreciate the role of AMH in PCOS, APNs must understand the

two-cell, two-gonadotropin model of estrogen synthesis, as well as how disruption of this process may lead to development of polycystic ovaries.[8] This model describes the working hormonal balance between the outer theca cell layer and the inner granulosa cell layer in the ovarian follicle; the former cell layer secretes androgens and the latter, estrogens. When luteinizing hormone (LH) stimulates cholesterol in the theca cells, androgen is released. Upon exposure to follicle-stimulating hormone (FSH), androgen is converted into estrogens in the granulosa cells.

When this two-cell, two-gonadotropin process is disrupted, a hormonal imbalance ensues, such that circulating LH concentrations exceed FSH concentrations. Ovarian androgen production increases, resulting in serum androgen excess. The increased androgen stimulates the growth of smaller antral follicles yet inhibits later follicular development and maturation.[9] Such arrest in follicle growth can lead to PCO morphology. These smaller antral follicles cannot be released via ovulation or subsequent luteinization.

Function of AMH

Anti-Müllerian hormone has been identified as the hormone secreted by sertoli cells in the male testes during embryonic sexual differentiation.[10,11] In females, AMH is a glycoprotein produced by the granulosa cells of antral follicles. The highest level of AMH secretion is evident in antral follicles ≥4 mm in diameter and continues to be expressed until the differentiation stage (8-9 mm), in which FSH selects a dominant follicle for future ovulation.[12] Evidence suggests that AMH inhibits follicular growth by inhibiting estrogen secretion in the antral follicles prior to FSH se-

lection. As a result, estrogen and AMH have an inverse relationship; AMH exerts a regulatory function by ensuring that not all primordial follicles are released at once.[13]

Levels of AMH fluctuate only minimally throughout the menstrual cycle, and not to the same extent as FSH and other pituitary and ovarian hormone levels. AMH levels are noted to be lower in women during pregnancy. These levels decline steadily after age 25 and are undetectable after menopause.[14] Information on whether AMH levels are affected by the use of hormonal contraception is conflicting.[15,16]

Current uses of AMH measurement

Because AMH is secreted by antral follicles prior to the differentiation stage, it is most often used as a clinical biomarker for ovarian reserve in infertility diagnosis and management and in detection of premature ovarian aging.[17,18] AMH is an excellent predictor of ovarian responsiveness in ovulation induction and in vitro fertilization, as well as a useful tool to help predict ovarian hyperstimulation, oocyte yield, and ovarian function pathology in an infertility setting.[13,19-21] In addition, AMH may be useful in assessing the need for fertility-preservation strategies and detecting post-chemotherapy or surgical damage to the ovarian reserve.[13,22]

Use of AMH measurement in diagnosing PCOS

A thorough history, physical examination, and select laboratory tests are important elements in determining the presence of androgen excess and ovulatory dysfunction—two of the three Rotterdam criteria used for PCOS diagnosis.[3] As described earlier, polycystic

ovaries, the third criterion, are identified via USG by the presence of more than 12 antral follicles measuring <10 mm and/or an increased ovarian volume (>10 mL) without a cyst or dominant follicle in either ovary. However, USG has potential shortcomings, including sensitivity of the machine, less-than-perfect operator technique, and subjective interpretation of the findings. In addition, transvaginal USG imaging may be inappropriate or less accurate in certain patient populations (e.g., obese persons or those who have never been sexually active).[3,4]

Determination of a patient's AMH level, an objective laboratory value, may help minimize the subjectivity of the USG findings. In several studies, a serum AMH level >18 pmol/L, when compared with USG, provided better sensitivity and specificity for PCO morphology in women who met Rotterdam criteria for PCOS.[5,23,24] Other studies have been performed to determine the optimal cutoff for the AMH value:

- A meta-analysis of data extracted up until January 2013 showed that an AMH value of 33.6 pmol/L was 82.8% sensitive and 79.4% specific in diagnosing PCOS in symptomatic women.[25]
- In 2013, a study of 60 infertile women with PCOS showed that an AMH value of 23.8 pmol/L was 98% sensitive and 93% specific in diagnosing PCOS.[26]
- Another 2013 study, conducted on 59 infertile women, 37 of whom had characteristics of PCOS, showed that an AMH level of 33 pmol/L was 95% sensitive and 95% specific in diagnosing PCOS.[1]
- In a study conducted in 2011 on 240 patients, an AMH value of 35.7 pmol/L was 92% sensitive

and 97% specific in identifying PCO morphology.[5]

These findings notwithstanding, a standard AMH level for diagnosing PCOS has yet to be established. Furthermore, several limitations preclude AMH from becoming widely utilized for PCOS diagnosis. First, lack of a universally accepted method and assay to measure AMH prevents it from becoming an established diagnostic tool for PCOS.[27] Second, because AMH declines with advancing age, the threshold for PCOS diagnosis may need to be modified through the life span.[28] Third, research involving the use of AMH level to diagnose PCOS in adolescents is limited.[27,29,30] Finally, the 2013 Endocrine Society guidelines do not include a recommendation for using AMH measurement as a routine diagnostic tool for PCOS.[3]

Although AMH level and oligo-anovulation are correlated, AMH has not been proven to be an acceptable indicator of ovulatory dysfunction or hyperandrogenism.[23] Hence, AMH level, if used, should be combined with other laboratory or clinical measures of hyperandrogenism and/or ovulatory dysfunction to maximize its diagnostic sensitivity and specificity. Furthermore, the role of AMH is unclear in diagnosing subtypes of PCOS, especially those that do not present with classic symptoms. Studies have suggested that ovulatory PCOS phenotypes, compared with anovulatory types, are associated with differing levels of serum AMH.[31]

Use of AMH measurement in gauging response to PCOS treatment

The goal of PCOS treatment is managing symptoms and minimizing co-morbidities. Proper management can reduce the risk for certain gynecologic cancers and infertility. Management should be both individualized and holistic and may include weight reduction through lifestyle modification and use of hormonal contraceptives, metformin, and gonadotropin/estrogen modulators. Current methods of monitoring the effectiveness of these management modalities include patient-reported symptom improvement and menstrual regulation, physical examination for reduction in signs of hyperandrogenism, measurement of insulin and glucose levels, and achievement of successful pregnancy outcome.

Many recent studies have been conducted to assess the relationship between various PCOS management modalities and patients' AMH levels; the *Table* (pp 38-39) lists a representative sample of such studies.[15,16,32-37] Additional research is needed to demonstrate the utility of these AMH measurements, especially as compared with current methods (e.g., clinical signs, patient-reported symptoms, other lab test findings) in making decisions about and evaluating the effectiveness of treatment.

Discussion

Based on what is known at this time, use of the AMH level is not recommended as a replacement for any component of the Rotterdam criteria in terms of diagnosing PCOS or as an assessment tool for monitoring the success of existing management modalities. However, AMH may be a useful supplemental tool for APNs because it is an objective and more reliable marker for diagnosing PCO morphology. Indeed, AMH can help providers who are not trained in pelvic or transvaginal USG in diagnosing PCOS. Although more research is needed in this area, AMH may be another component of PCOS diagnosis and management in the future.

Conclusion

Although the Rotterdam criteria are the gold standard for diagnosing PCOS, concern regarding the subjective nature of polycystic morphology on USG has been voiced over the years. An AMH value >35 pmol/L may have the highest sensitivity and specificity in terms of indicating polycystic ovaries. However, data supporting the use of AMH levels to make treatment choices or to monitor the effectiveness of such treatments in females with PCOS are inconclusive. At the very least, findings from studies assessing changes in AMH levels related to specific treatment modalities may offer more insight into the pathophysiology of this complex endocrine disorder. ●

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Table. Sample studies representative of effect of specific PCOS treatment modalities on serum AMH levels[15,16,32-37]

Source	Purpose	Study design/sample	Results	Conclusions
Somunkiran et al, 2007[15]	To examine the influence of hormonal suppression with OC therapy on serum AMH levels in women with PCOS and in women with normal menstrual cycles	Prospective study; 30 women with PCOS, 15 women with normal menstrual cycles	No significant decrease in AMH after 6 months of OC therapy in either group; significant reductions in ovarian volume and follicle number and size in both groups	Because OC use did not significantly change serum AMH levels, AMH may be considered as a PCOS diagnostic marker in patients on OCs
Panidis et al, 2011[16]	To assess the impact of metformin and two different OCs containing cyproterone acetate or drospirenone on AMH levels in women with PCOS and hyperandrogenism	Prospective, randomized study; 45 women with PCOS and hyperandrogenism assigned to an OC containing EE 35 mcg and cyproterone acetate 2 mg (group A), EE 30 mcg and drospirenone 3 mg (group B), or metformin 850 mg BID (group C)	At 3 and 6 months, significant decrease in AMH, LH, FSH, T, androstenedione, and 17-OHP and an increase in SHBG in Group A; significant decrease in LH, FSH, and T and an increase in SHBG, with no significant change in AMH, 17-OHP, or androstenedione in Group B; no significant change in AMH, LH, FSH, T, androstenedione, 17-OHP, or SHBG in Group C	AMH levels were significantly reduced in Group A, likely because of a decrease in androgens and suppression of gonadotropins
Neagu & Cristescu, 2012[32]	To assess AMH as a prognostic marker for metformin therapy efficiency in treatment of women with infertility and PCOS	Prospective study; 11 women with infertility and PCOS	Ovulation restored and AMH levels significantly decreased in all participants after 2 months of metformin	AMH levels in women with infertility and PCOS given metformin were a useful predictor of treatment efficacy
Tomova et al, 2011[33]	To evaluate levels of AMH in women with PCOS before and after metformin therapy	Prospective study; 22 women with PCOS and 20 women without PCOS as controls	Of 17 women with PCOS who completed 6 months of metformin, 13 responded with restoration of normal menstrual cycles and decreased AMH levels; compared with the 4 non-responders, these 13 women had significantly greater BMI, WC, body fat, and BP	Obese women with PCOS, versus those with lower BMIs, were more likely to respond to metformin therapy and have decreases in AMH levels

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Table. Sample studies representative of effect of specific PCOS treatment modalities on serum AMH levels[15,16,32-37]

Source	Purpose	Study design/sample	Results	Conclusions
Kriseman et al, 2015[34]	To determine whether AMH levels are associated with BMI in patients diagnosed with infertility and PCOS	Retrospective cohort study; 489 infertile women, 104 of whom were diagnosed with PCOS	Overall, no association between BMI and AMH; significant inverse relationship between BMI and AMH in participants with PCOS; in PCOS participants, average AMH significantly higher in those with BMI <25 than in those with BMI >25	This study contributes to understanding of potential differences in infertility treatment response in the subtypes of OW and lean women with PCOS
Piouka et al, 2009[35]	To compare AMH levels among OW/O and normal weight women with 4 different PCOS phenotypes	200 women with PCOS (100 normal weight and 100 OW/O), classified into 4 phenotypes (25 normal weight and 25 OW/O in each phenotype group): (1) ANOV, HA, and PCO; (2) ANOV and HA; (3) HA and PCO; and (4) ANOV and PCO, along with 50 women without PCOS (25 normal weight and 25 OW/O)	AMH levels significantly higher in all 4 PCOS groups versus controls; AMH levels significantly higher in PCOS groups 1 and 2 versus groups 3 and 4; AMH levels significantly higher in normal weight women versus OW/O women in all 4 PCOS groups and the control group	Differences in AMH levels among women with the 4 different PCOS phenotypes may reflect severity of PCOS (groups 1 and 2 considered to be more severe types than groups 3 and 4); however, AMH is inversely affected by obesity in women with or without PCOS
Thomson et al, 2009[36]	To assess whether baseline and/or change in AMH levels with weight loss predict improvements in reproductive function in OW/O women with PCOS	Prospective study; 52 OW/O women with PCOS and reproductive impairment	26 participants who had improvements in reproductive function after 20-week weight-loss program had lower baseline AMH levels and experienced greater weight loss than did 26 participants who did not demonstrate improved reproductive function; AMH did not change with weight loss in either group	Weight loss interventions may result in improved reproductive function in OW/O women with PCOS but no change in AMH levels
Mahran et al, 2013[37]	To investigate the impact of high AMH levels on the outcome of CC ovulation induction in women with PCOS	Prospective cohort study; 60 anovulatory women with PCOS	AMH levels significantly lower in CC ovulation induction responders than in non-responders; significant gradient increase in AMH with increasing dose of CC needed to achieve ovulation; pregnancy rates significantly higher in women with low AMH (<3.4 ng/mL) than in women with AMH >3.4 ng/mL	Women with PCOS and higher AMH levels (>3.4 ng/mL) seemed to be more resistant to CC and may require higher starting dose

17-OHP, 17-hydroxyprogesterone; AMH, anti-Müllerian hormone; ANOV, anovulation; BMI, body mass index; BP, blood pressure; CC, clomiphene citrate; EE, ethinyl estradiol; FSH, follicle-stimulating hormone; HA, hyperandrogenism; LH, luteinizing hormone; OC, oral contraceptive; OW/O, overweight/obese; PCO, polycystic ovaries; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; T, testosterone; WC, waist circumference.