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College of Nursing and Professional Disciplines

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PERMISSION

Title

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Abstract

Anti-müllerian hormone (AMH) has been presented as a reliable biological marker for polycystic ovary syndrome (PCOS). Currently, PCOS, the leading cause of infertility, is diagnosed primarily by clinical features using the 2003 Rotterdam criteria. The lack of biological markers often prolongs the diagnosis of PCOS, delaying treatment and increasing the risk for developing T2DM and metabolic syndrome. Furthermore, this delay in treatment is frustrating to women and decreases their trust and satisfaction in their primary care provider. The foundation for this literature review was determined by an outpatient visit with a 65-year-old female who presented for a medication follow up for poorly controlled Type 2 diabetes (T2DM) and hypertension. This contributed to the need for a literature review of AMH as a diagnostic marker for PCOS. This review was conducted using PubMed and CINAHL. The comprehensive search resulted in 15 relevant articles. Thirteen of these articles found AMH as a reliable diagnostic tool for PCOS. However, it lacks international standardization and further studies are needed to determine the AMH threshold for diagnosis of PCOS.

Keywords: anti-müllerian hormone, polycystic ovary syndrome, diagnosis of polycystic ovary syndrome

Background

Polycystic ovary syndrome (PCOS) is the leading cause of infertility, afflicting approximately 6% of women during their reproductive years (Wiweko et al., 2014). Women with PCOS often suffer from menstrual disorders and infertility characterized by anovulatory cycles and hyperandrogenism. Clinical features include hirsutism, acne, menstrual irregularities, obesity, dyslipidemia, and insulin resistance (Wiweko et al., 2014). These conditions increase the risk of T2DM, coronary heart disease, cardiovascular diseases, and endometrial cancer (Ali,
2015). Additionally, some women with PCOS have decreased satisfaction with their healthcare (Lin et al., 2018). Surveys have shown that patients have reported long delays in PCOS diagnosis, had less confidence in their primary care providers, and considered their providers less qualified to treat their PCOS (Lin et al., 2018).

PCOS is diagnosed clinically and by exclusion of other conditions. Clinical features are grouped into three diagnostic criteria utilizing the 2003 Rotterdam criteria (The Rotterdam ESHRE/ASRM, 2004): oligo-and/or anovulation (OA), hyperandrogenism (HA), and polycystic ovaries (PCO) demonstrated on ultrasound. The diagnosis of PCOS is made with the presence of a minimum of two criteria after exclusion of other diseases. Laboratory testing is limited regarding diagnosis. Recommended biochemical testing includes total testosterone and 17-hydroxyprogesterone. Tests to exclude other conditions are human chorionic gonadotropin, prolactin, thyroid-stimulating hormone, and follicle-stimulating hormone. Tests that are beneficial in certain populations, but are not routinely recommended, are free testosterone, DHEAS, and androstenedione. The anti-müllerian hormone (AMH) is currently not included in the evaluation of PCOS, partially due to a lack of international standard (Barbieri & Ehrmann, 2018).

AMH is a promising biological marker for PCOS as the level is not altered by the menstrual cycle or oral contraceptives (Wiweko et al., 2014). It is a glycoprotein and a member of the transforming growth factor- beta (TGF-β) family. AMH is produced by granulosa cells surrounding preantral and antral follicles less than 8 mm (Wiweko et al., 2014). AMH suppresses follicle-stimulating hormone (FSH), limiting follicular growth and luteinizing hormone (LH) receptors. It also decreases the follicles’ sensitivity to FSH, increasing the number of antral
fOLLICLES. THEREFORE, AMH REGULATES FOLLICULOCENGESIS AND SERVES AS A BIOMARKER FOR OVARIAN RESERVE AND OVARIAN DYSFUNCTION, SUCH AS PCOS.

**Case Report**

For this independent study, a patient presented with diabetes. The topic chosen pertaining to diabetes was AMH and the diagnosis of PCOS. Insulin resistance and T2DM are common among women with PCOS. Perhaps with better PCOS diagnostics, treatment could be started earlier, preventing future diabetes and complications.

The patient examined during this case study was a 65-year-old female patient. The patient was here for a 6-month follow-up regarding her diabetes. She had been compliant with her medications. She checked her blood sugars two to three times a week, both fasting and post-prandial. Her morning fasting blood sugars were approximately 170 to 220. She had no complaints other than some mild weight gain. She admitted to having no regular exercise due to the cold winter months and recently retiring. Her last ophthalmology exam was two weeks ago.

**History**

Current medications include: Glipizide 10 mg daily, Lisinopril 10 mg daily, Toprol XL 50 mg daily, Zocor 20 mg daily, Janumet 50/1000 mg twice daily, Aspirin 81 mg daily, and a multivitamin. She had no known allergies. Past medical history included obesity, hyperlipidemia, DM type II, and actinic keratosis. Past surgical history included cataract, colon polyp removal and carpal tunnel. Social history included recently retiring, only social alcohol use, no tobacco or recreational drug use, and her marital status was not disclosed. There was no pertinent family history reported. She was post-menopausal. Her health maintenance included influenza vaccine in October 2018, tetanus vaccine in February 2003, and she had not received PSV and PPSV 23. Her last colonoscopy was in 2003 and date of last mammography was unknown.
Review of Systems

A complete review of systems was completed. All systems were negative, except for the complaint of fatigue. The patient stated that she has no trouble sleeping or falling asleep. She occasionally takes afternoon naps and denied any feelings of depression.

Physical Exam

Vital signs were as follows: blood pressure of 138/80, heart rate of 72 beats per minute, respiratory rate of 18 breaths per minute, and a weight of 122 kg with a BMI of 36.5. A CMP, Hgb A1c, lipid panel, urine creatinine and microalbumin with ratio was completed. The patient was fasting. Abnormal labs included triglyceride of 167, HDL of 39, Hgb A1c of 9.5, glucose of 324, and bilirubin of 1.1.

A comprehensive physical exam was completed, including a fundoscopic and foot exam. Monofilament exam was up to date and deferred at that visit. The assessment was within normal limits and as follows: The patient was alert and active, and in no acute distress. She had normal S1 and S2 heart sounds with no murmurs, clicks, or rubs. The radial and post-tibial pulses were plus two and symmetrical. The lung sounds were clear throughout and without adventitious sounds. The skin was warm and dry. No lesions or ulcers on the lower extremities were noted. The rest of the physical examination was unremarkable.

Management of Care

Vital signs, lab results, and medications were reviewed with the patient. We discussed that her blood sugar and lipids were elevated. Her blood pressure was within the target goal of less than 140/90. Regarding her elevated blood sugar, the patient was agreeable to discontinuing glipizide and starting insulin. The patient met with a diabetic educator after the visit to discuss insulin administration, blood sugar monitoring, diet, and exercise. We discussed the benefits of
starting a statin. The patient refused starting a statin and preferred to try diet and exercise first. We added a TSH with reflex, CBC, and ferritin to labs for fatigue.

The patient received her PSV 13 and Tdap vaccines during the visit. A colonoscopy and mammogram were ordered for cancer screening.

**Follow Up**

The patient met with the diabetic educator after the visit. She will plan to record her blood sugars as directed and follow up with the diabetic educator via telephone weekly for four weeks. A one-month follow-up visit with this provider was scheduled to review blood sugars, blood pressure, and medications. This provider will notify the patient of the laboratory results once they are available. The patient understood and agreed with the plan.

**Literature Review**

The purpose of this literature review was to determine if AMH is a reliable marker for the diagnosis of PCOS. PubMed and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were used. The first search was completed using PubMed with the keywords “anti-müllerian hormone,” “polycystic ovary syndrome,” and “diagnosis of polycystic ovary syndrome.” The search was limited to articles that were printed in the last five years, clinical trial, controlled clinical trial, meta-analysis, randomized controlled trial, review, systemic reviews, species human, and English. This resulted in 176 articles. Of these articles, 15 were relevant to this systematic review. A second search was conducted through CINAHL using the same keywords. Eight articles were found. One of which was a repeat article, and seven were not specific to this topic.

For the grading of evidence, the Melnyk Pyramid was used (NOVA, 2019). This tool was chosen for its straightforward categorization of levels and ease of use. The hierarchy of levels
begins at Level I having the most validity of evidence and continuing down to Level VII which has the least supporting evidence and consists mainly of expert opinions. Nursing: Melnyk Pyramid has a clear description and algorithm for further details (NOVA, 2019).

The results of this literature review synthesizes one Level 1 article (Wang, Niu, Kong, Guo, & Sun, 2017), ten Level III articles (Aydogmus, Kelekci, Elmali, & Aydogmus, 2018; Bhide & Homburg, 2016; Cassar et al., 2014; König et al., 2014; Safier, Grossman, Chan, Sauer, Lobo, & Douglas, 2016; Sahmay et al., 2014; Sexena, Ramani, & Slingh, 2018; Sopher et al., 2014; Wongwananuruk et al., 2018; Yue, Lu, Li, Zhang, & Ying, 2018;), three Level IV articles (Carmina, Campagna, Fruzzetti, & Lobo, 2016; Tal et al., 2014; Wiweko et al., 2014), and one Level VII (Goodman, Cobin, Futtweit, Glueck, Legro, & Carmina, 2015).

**Polycystic ovary syndrome**

The definition of PCOS is continuously evolving and the cause largely unknown. The articles under review agree that PCOS is a diagnosis of exclusion and includes a spectrum of clinical features: “cutaneous signs of hyperandrogenism (hirsutism, acne, acanthosis nigricans), menstrual irregularity (oligo-/amenorrhea, or irregular bleeding), polycystic ovaries (one or both), obesity and insulin resistance,” (Rosenfield, 2018, para. 5). Providers can diagnose PCOS using these classical signs and polycystic ovarian morphology on transvaginal ultrasound (TVUS). However, not all women present with classical signs, making diagnosis difficult. This has led to significant controversy over the diagnostic criteria of PCOS.

Current recommendation utilizes the Rotterdam criteria for diagnosis of PCOS (The Rotterdam ESHRE/ASRM, 2004). This criterion was used throughout the articles as a control diagnostic to compare AMH assay accuracy. However, it is highly subjective in that it is based on history and physical (Rosenfield, 2018).
Four phenotypes of PCOS have been identified. Phenotype A is characterized by OA, HA, and PCO; B is HA and OA; C is HA and PCO; and D is OA and PCO (Wiweko et al., 2014).

Biochemical testing includes total testosterone which is indicated in women with signs of hyperandrogenism. It is best assessed using liquid chromatography – tandem mass spectroscopy (LC-MS/MS). A range of 45 to 60 ng/dL is indicative of upper limits of normal (Rosenfield, 2018). A result greater than 150 ng/dL needs further evaluation for more serious conditions. Serum 17-hydroxyprogesterone should be tested in the morning during early follicular phase in women with spontaneous menstrual cycles and on a random day for those who are anovulatory (Rosenfield, 2018). Neither of these tests alone are diagnostic of PCOS. They are only diagnostic in conjunction with clinical signs as designated by the Rotterdam criteria (The Rotterdam ESHRE/ASRM, 2004).

AMH as a diagnostic tool for PCOS

Studies have demonstrated the efficacy of utilizing AMH as a diagnostic tool. Of the 15 articles reviewed, 13 consistently showed high levels of AMH correlating with PCOS. Wiweko et al. (2014) demonstrated in their study that women with an AMH of greater than 4.45 ng/mL had PCOS. This study further posited that the level of AMH reflects which phenotype of PCOS the patient has. The authors noted a positive correlation between hyperandrogenism and AMH levels, which they observed also places the patient at greater risk for metabolic or cardiovascular disease. This risk was highest in phenotypes A and B. Additionally, AMH had a positive correlation with luteinizing hormone, total testosterone, dehydroepiandrosterone sulfate, insulin resistance, free androgen index, and LDL cholesterol levels, and a negative correlation with HDL cholesterol levels (Tal et al., 2014; Wiweko et al., 2014).
Sahmay et al. (2014) concluded that AMH levels are useful diagnostic markers for PCOS and correlated with conventional diagnostic criteria as defined by the Rotterdam criteria, National Institutes of Health (NIH), and Androgen Excess Society (AES) criteria (Azziz et al., 2009; NIH, 2019; The Rotterdam ESHRE/ASRM, 2004). Compared with the Rotterdam criteria, elevated AMH (with a cut-off level of 3.8 ng/mL) in combination of OA and/or HA showed 83% sensitivity and 100% specificity; the NIH showed 83% sensitivity and 89% specificity, and the AES showed 82% sensitivity and 93.5% specificity. These percentages, albeit slightly higher than most, are comparable to other articles reviewed.

Two articles within this review concluded that AMH should not be used as a PCOS diagnostic. Among these was Wang et al. (2017), the only Level 1 systematic review found. These authors noted that AMH and AMHR2 appear not to be associated with PCOS. However, the review was limited to five articles in which four of them were greater than 11 years old.

The second article of note was Carmina et al. (2016). This was a Level IV retrospective matched controlled study of 113 cases and 47 controls. These authors concluded that AMH was not a helpful marker for all subjects of PCOS; however, it may have some value for patients who are anovulatory. Furthermore, these authors postulated that ultrasound parameters for follicle per ovary (FPO) of greater than 22 was the single best criterion and highly sensitive to all PCOS phenotypes.

**AMH cut-off level**

Utilizing AMH as a diagnostic marker is hampered by the lack of set guidelines. Currently, the panel of American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society agree that greater than 4.5 ng/mL
should be the value used to diagnose PCOS (Goodman et al., 2015). Wiweko et al. (2014) found 4.45 ng/mL the optimal threshold to maintain a sensitivity of 76.1% and a specificity of 74.6%.

Of the 15 articles within this review, 12 listed their cut-off level for AMH. The cut-off levels with the highest sensitivity and specificity were an average of 4.5 ng/mL and a mode of 4.7 ng/mL. Yue et al. (2018) was the only study with a significant outlier. This study listed 5.89 ng/mL as the cut-off level for ages 30 to 39 years. However, they also listed 8.16 ng/ml for ages 20 to 29 years. Despite this difference, the cut-off level is consistent throughout the studies and recommendations. This confirms that the previous recommendation of 4.5 ng/mL by the panel of experts would be advisable for diagnosis of PCOS.

**International standardization**

The analysis of AMH is gaining recognition for its clinical purpose in differentiating between causes of secondary oligo-amenorrhea with documented accuracy. AMH levels have been shown to increase two to three times in women with PCOS (Li et al., 2012). Additionally, AMH becomes significantly reduced in premature ovarian failure (POF) and stay constant in hypogonadotrophic hypogonadism and hyperprolactinemia compared to ovulatory women (Li et al., 2012).

Serum testing of AMH has been available worldwide by two ELISA kits. These kits are manufactured by Diagnostic Systems Laboratories, Inc. (DSL) and Immunotech (IOT), which are subsidiary companies of Beckman Coulter, Inc. Beckman Coulter has developed a new ELISA kit called “AMH Gen II ELISA” to replace the former two kits. Beckman Coulter states, “the AMH Gen II ELISA kit uses the same antibody as in the DSL kit but the standards of the IOT assay kit,” (Li et al., 2012, para. 4).
A study conducted by Li et al. (2012) demonstrated significant differences of AMH values between the three kits, with the Gen II reporting 35% higher values than the old kits. This discrepancy demonstrates a need for standardization so AMH can be available for clinical application. Furthermore, it is important to note that there are two different units of measurement: ng/mL and pmol/l. In the 15 articles analyzed within this review, eleven used ng/mL, one used pmol/l, and three did not mention a unit of measurement. For conversion of units: 1 ng/ml equals 7.18 pmol/l (Li et al., 2012).

Conclusion

This literature review concluded that 13 of the 15 articles were in favor of utilizing AMH levels for the diagnosis of PCOS. Wiweko et al. (2014) are in strong favor and state that AMH levels could be used as an alternative for PCOS diagnosis. Conversely, another article, Carmina et al. (2016), states that AMH is only beneficial in anovulatory women. However, most of the articles concluded that AMH levels, especially in conjunction with conventional criteria, are beneficial as a diagnostic.

There is a consensus for the need for further randomized control trials on this subject. These studies should utilize AMH Gen II ELISA for testing and to determine the significance of laboratory values. Furthermore, establishing a standardized cut-off level of AMH for the diagnosis of PCOS is essential for clinical use.

Learning Points

AMH is produced by the granulosa cells of the pre-antral and antral follicles of the ovary. A positive correlation of high AMH levels and PCOS has been documented. While AMH is yet to be fully endorsed as a diagnostic, it is gaining evidence for this purpose. It is hindered by a lack of guidelines and international standardization.
• AMH has a positive correlation with luteinizing hormone, total testosterone, dehydroepiandrosterone sulfate, insulin resistance, free androgen index, and LDL cholesterol levels, and a negative correlation with HDL cholesterol levels

• AMH is a useful marker for the diagnosis of PCOS in conjunction with conventional criteria

• There are no set guidelines or cut-off levels for AMH as a diagnostic of PCOS. However, the consensus among review is 4.5 ng/mL as the cut-off for diagnosis

• There is a need for further studies using the new AMH Gen II ELISA for standardization
References


diagnosis-of-polycystic-ovary-syndrome-in-adolescents


