



Clinical application of serum anti-Müllerian hormone in women

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Anti-Müllerian hormone (AMH), a peptide growth factor of the transforming growth factor- β family, is a reliable marker of ovarian reserve. Regarding assisted reproductive technology, AMH has been efficiently used as a marker to predict ovarian response to stimulation. The clinical use of AMH has recently been extended and emphasized. The uses of AMH as a predictive marker of menopause onset, diagnostic tool for polycystic ovary syndrome, and assessment of ovarian function before and after gynecologic surgeries or gonadotoxic agents such as chemotherapy have been investigated. Serum AMH levels can also be affected by environmental and genetic factors; thus, the effects of factors that may alter AMH test results should be considered. This review summarizes the findings of recent studies focusing on the clinical application of AMH and factors that influence the AMH level and opinions on the use of the AMH level to assess the probability of conception before reproductive life planning as a "fertility test."

Keywords: Anti-Müllerian hormone; Fertility; Ovarian reserve; Polycystic ovary syndrome; Surgery

Introduction

Anti-Müllerian hormone (AMH), a peptide growth factor of the transforming growth factor- β family [1], is well known for its role in sexual differentiation. In men, AMH is secreted from the Sertoli cells of the testes, promotes Müllerian duct regression, and initiates male phenotypic development. Without AMH, the Müllerian ducts differentiate into the uterus, one-third of the vagina, and oviducts [2,3].

When primordial follicles are recruited, AMH is initially produced in granulosa cells [4]. AMH expression continues to increase until primordial follicles have developed into small antral follicles approximately 4–6 mm in size [5]. In a study of AMH-knockout (AMHKO)

mice, female AMHKO mice showed faster recruitment of primordial follicles and earlier depletion of follicles than wild-type female mice, suggesting that AMH inhibits the initiation of primordial follicular growth and prevents premature follicular exhaustion [4,6,7]. Further, Nilsson et al. [8] found that AMH had an inhibitory effect on factors such as stem cell factor (kit ligand) and basic fibroblast growth factor, which are known to stimulate primordial follicular recruitment. When follicles have reached 8 mm, AMH levels rapidly decrease, becoming undetectable during follicle stimulating hormone (FSH)-dependent stages or in follicles showing signs of atresia [6,9]. Antral follicles producing less AMH are more sensitive to FSH, which allows continued growth and ovulation [10]. AMH may down-regulate the aromatizing capacity of granulosa cells, which reduces estradiol (E_2) production until final follicular selection [11-13]. When follicles have grown sufficiently, AMH levels rapidly decrease, while E_2 production increases rapidly thereafter [14]. This transition of the E_2 level correlates with dominant follicular selection. E_2 has opposite action through estrogen receptor (ER) β and ER α on AMH expression. Because dominant follicles have more ER β than ER α , E_2 inhibits AMH transcription via ER β [14].

As many women of reproductive age delay childbearing, interest in

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ovarian function and fertility is increasing. Regarding assisted reproductive technology (ART), AMH has been used efficiently to predict ovarian response to stimulation. The clinical use of AMH was recently extended and emphasized. In this review, we discuss AMH in relation to ovarian function, fertility, and various factors and conditions to consider before its clinical application and interpretation.

Serum AMH level and its role as an ovarian reserve marker in women

In women, AMH is produced and secreted from ovarian granulosa cells from approximately 36 weeks of gestation to menopause [15,16]. AMH level is very low and barely detectable in the neonatal period; however, a modest increase occurs a few weeks after birth, and the level peaks at around 25 years of age [2]. As the pool of small growing follicles is in parallel with the total number of primordial follicles, AMH reflects ovarian reserve [17]. During the early follicular phase, the antral follicle count (AFC) and AMH levels are correlated [18]. Unlike other biomarkers for ovarian reserve, such as FSH and inhibin B, AMH levels fluctuate minorly during normal menstrual cycles. Tsepelidis et al. [19] explained that AMH secretion is mostly affected by the early follicular recruitment rate of the follicular pool, which is independent of the menstrual cycle. This Serum AMH level stability regardless of the menstrual cycle makes it much easier to use it to evaluate ovarian reserve than other markers. Although the individual variability of AMH is low, differences in the degree of fluctuations with age have been observed [20,21]. Studies showed an inverse correlation with age and AMH fluctuation degree, which indicated that younger patients with usually high ovarian reserves had greater fluctuations in AMH levels.

As the ovarian follicular pool decreases with age, markers for ovarian reserve also change. The FSH level increases after 35 years of age [22], while the inhibin B level decreases with age [23-25]. Until 40 years of age, neither FSH nor inhibin B shows a definite correlation with age. These endocrine changes seem to occur when the number of follicles significantly decreases [26]. In Korea, Lee et al. [27] described an age-specific model of AMH that may be helpful for evaluating the ovarian reserve of infertile women. However, an absolute age-specific AMH level to evaluate ovarian reserve at that time is somewhat limited. A nomogram of patients of other ethnicities ranging from infancy to adulthood has been reported [28,29]. Briefly, AMH showed a longitudinal decline over time after peaking in the mid-twenties, suggesting that AMH reflects the decline in the ovarian follicular pool with age better than any other ovarian reserve markers [26,27].

Clinical application of AMH

1. Use as a prediction marker of ovarian response in controlled ovarian stimulation

Serum AMH levels have been used to predict the quantitative and qualitative aspects of controlled ovarian stimulation (COS). About one-third of women who undergo *in vitro* fertilization yield a larger number of oocytes than expected [11,30,31]. These excessive responses may lead to a lower probability of pregnancy, poorer-quality embryos, or even cycle cancellation [32-38]. In an individual patient data meta-analysis of 4,786 women, the prognostic power for predicting an excessive ovarian response using serum AMH level, AFC, and age have been suggested [39]. According to their model, serum AMH level, AFC, and patient age showed an area under the receiver operating characteristic curve (AUC) of 0.85. Even without age, the use of AMH level and AFC for predicting excessive response in COS had similar accuracies. These findings indicate that serum AMH level and AFC may present good predictive accuracy for excessive response with adding value to female age.

High basal AMH levels may also increase a patient's risk of developing ovarian hyperstimulation syndrome (OHSS). Four prospective studies that included large numbers of subjects reported relevant values of AMH for predicting hyper-response and OHSS [40-43]. One study showed that the cutoff value of 3.36 ng/mL measured by Diagnostic System Laboratories predicted OHSS with 90.5% sensitivity and 81.3% specificity [42].

In addition, AMH is used to predict poor responders in COS; however, there is no clear standard definition of a poor responder [44]. Several authors studied the usefulness of AMH for predicting a poor response to gonadotropin. For example, Lee et al. [45] investigated the cutoff level of serum AMH for predicting poor (number of oocytes retrieved, ≤ 3), normal (4–19), and high responders (≥ 20). Especially for predicting poor responders, the cutoff level was 1.08 ng/mL, with 85.8% sensitivity and 78.6% sensitivity. These results can be used to determine the recombinant human FSH starting dose and predict the final oocyte yields and develop a nomogram that could predict oocyte yield. Moon et al. [46] developed nomograms that could predict oocyte yield using age, basal serum FSH level, serum AMH level, and AFC in a Korean population. Briefly, AMH measurement helps predict the extremes of ovarian response to gonadotropin stimulation. Many studies have unsuccessfully attempted to obtain results of the prediction value of AMH for qualitative aspects of ART, such as oocyte quality, embryo quality, and implantation and pregnancy rates [47].

2. Use as a marker for predicting age at menopause

Predicting age at menopause may help women prepare their post-

menopausal life as well as their late reproductive life, especially for women concerning early menopause. However, no marker can currently be used to predict the exact age of menopause. Since AMH reflects the gradual decline in reproductive capacity with age, it is receiving increasing attention as a potential marker for menopause [26,48-50].

Broer et al. [51] presented a model that related an age-specific AMH level percentile with the predicted age at menopause. For example, a 30-year-old woman with an AMH level close to 0.15 ng/mL was categorized under the fifth percentile (p); therefore, predicted mean age at menopause was 48.8 years (p5 to p95, 42.1–53.0 years). They suggested that menopause timing could be individually calculated. However, as the range of the predicted menopausal age is too wide to accurately predict the exact age, its application in clinical practice may be limited.

Whether AMH could become a clinically valuable indicator of the risk of early menopause has not been assessed. Several population-based studies conducted to date have included sufficient numbers of women undergoing early natural menopause to evaluate this relationship. A recent prospective study of 327 women with early menopause showed that the mean AMH level was significantly lower in cases (0.40 ng/mL) than in controls (1.9 ng/mL; $p < 0.001$) [52]. Every AMH level decrease of around 0.10 ng/mL was related with a 14% increased risk of early menopause ($p < 0.001$). Furthermore, a meta-analysis of 2,596 female patients (of whom 1,077 were menopausal) showed that the combination of AMH and age was more reliable in the prediction of early menopause than age alone [53]. Despite all the studies, more accurate threshold for AMH level needs to be defined, and other variables, such as family history of early menopause, maternal age at menopause, and lifestyle factors (smoking, body mass index [BMI], use of alcohol, and parity) should also be considered.

3. Factors that affect serum AMH levels

AMH is a test that represents ovarian reserve but is not dependent on the menstrual cycle. Nonetheless, it can be affected by environmental and genetic factors [54-57]. These factors may lead to errors in the interpretation of serum AMH levels in clinical practices. One important element in the clinical setting is awareness of the factors that affect serum AMH levels. Here we describe the most common issues associated with AMH level variations in women.

1) Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the most common ovulatory disorders. The serum AMH level is two- to three-fold higher among women with PCOS than among normo-ovulatory women, in line with the increased number of small antral follicles in PCOS

[58,59]. AMH production is highly increased (by up to 75-fold) in granulosa cells of anovulatory polycystic ovaries compared to that in granulosa cells in normal controls [60]. Dewailly et al. [61] noted that the number of small follicles (2–5 mm in size) was positively correlated with the severity of menstrual disturbances in PCOS, especially in women with amenorrhea. Using a threshold AMH level of 11.4 ng/mL, serum AMH could predict amenorrhea with 91.7% specificity and 79.4% sensitivity in PCOS [62]. Taken together, these findings imply that anovulatory patients with PCOS have an increased number of small antral follicles producing AMH, leading to an AMH-dominant microenvironment, which interferes with the actions of FSH on follicles, leading to anovulation and amenorrhea.

Factors related to the pathophysiology of PCOS, such as increased luteinizing hormone (LH) levels, increased androgen levels, and insulin resistance may be associated with elevated serum AMH levels. LH is known to increase AMH production up to four-fold in granulosa cells of PCOS ovaries and elevates AMH expression in the granulosa cells of oligo- or anovulatory PCOS women [60,63], implying a role of LH in excessive AMH expression and follicular arrest. Androgens stimulate the FSH-independent stages of follicular development [64,65] and may increase AMH production. A positive correlation was noted between fasting insulin and AMH levels in PCOS and non-PCOS women [66]. In contrast, an independent inverse relationship was identified between insulin resistance and AMH in women without PCOS, probably by an abnormal effect of insulin action on AMH secretion from granulosa cells [67]. The exact relationship between insulin resistance and AMH has not been fully elucidated.

2) History of ovarian surgery

Several histologic analyses have shown that normal ovarian tissues can be unintentionally removed in most cases of ovarian cystectomy, especially for ovarian endometrioma [68-71]. Electrocoagulation may also damage the ovarian blood supply and stroma [68,72]. Postoperative damage to the ovarian reserve can be assessed by comparing pre- and postoperative AMH levels [73]. Chang et al. [74] prospectively evaluated a series of declining changes in serum AMH levels after laparoscopic ovarian cystectomy. The median AMH level at 3 months postoperative was about 65% that of the preoperative level (2.23 ng/mL before surgery vs. 1.50 ng/mL at 3 months postoperative).

It is unclear whether the postoperative decline in AMH is comparable between endometrioma and other benign ovarian cysts. A recent study reported that women with endometriomas had considerably lower baseline AMH levels than women without endometriosis [75]. The presence of an endometrioma may contribute to a decline in ovarian reserve [76]. Therefore, patients with already diminished ovarian reserve should be warned before surgery about the possibili-

ty of premature ovarian insufficiency after surgical intervention and the need for fertility preservation. Clinicians should consider that the AMH level could be low in women with a history ovarian surgery. Ovarian cyst bilaterality is the most significant factor in predicting AMH level decreases after laparoscopic surgery ($p < 0.001$) [77]. Thus, patients with low preoperative AMH levels should be managed more carefully.

3) Chemotherapy

Since chemotherapy is detrimental to female fertility, researchers have attempted to predict the risks of decreased ovarian reserve in women with planned chemotherapy. A prospective study of women treated with chemotherapy for early breast cancer showed that long-term ovarian function after treatment was predictable using serum AMH levels before treatment. This predictive value of serum AMH level was superior to age as well as inhibin B and FSH levels [78]. The primary cutoff values of the pre-chemotherapy AMH level were < 0.53 ng/mL for predicting amenorrhea and > 2.84 ng/mL for predicting ongoing menses.

The role as a predictive marker for ovarian function recovery after ovarian protection by gonadotropin-releasing hormone (GnRH) agonists during chemotherapy in young breast cancer patients was emphasized [79]. If the pretreatment AMH level is > 3.26 ng/mL, the AMH level 1 year after GnRH agonist therapy is expected to be at least 1 ng/mL regardless of age or pretreatment FSH level. Meanwhile, Kim et al. [80] determined that the post-chemotherapy AMH level is an independent predictor of ovarian function recovery among breast cancer patients with amenorrhea after chemotherapy. An AMH level ≥ 0.8 ng/mL may reflect the recovery of menstruation for 5 years. Studies of the role of the prechemotherapy AMH level in predicting the restoration of menstruation and fertility after treatment will continue since fertility preservation is very important in these patients.

4) Oral contraception

Ovarian reserve parameters are lower among users than non-users of combined oral contraceptives (COC) [81-83]. A cross-sectional study of a total of 887 women aged 19–46 years using COC showed decreased overall ovarian reserve parameters, i.e., ovarian volume, AFC, and AMH level significantly decreased by 50% (95% confidence interval [CI], 45.1%–53.7%), 18% (95% CI, 11.2%–24.8%), and 19% (95% CI, 9.1%–29.3%), respectively [84]. They found a considerable decrease in the number of small antral follicles with age and detected a similar shift toward smaller AFC subclasses in women using COC. The diminished overall number of antral follicles and suppressed FSH could explain the decreased AMH levels in COC users versus non-users. For this reason, clinicians should be cautious when

assessing ovarian reserve in COC users. The actual AMH level and AFC are probably 20% higher than the measured values in COC users. The suppressive effect of COC is known to recover within 3–6 months [81,85]. When counseling COC users about their reproductive lifespan and fertility status, AMH level or AFC alone should not be used, but it could be used as a sub-reference value.

5) Obesity

Obesity is well known for its negative effects on reproduction, including ovulatory dysfunction, infertility, miscarriage, and other reproductive complications [86]. A cross-sectional study of AMH levels in relation with BMI at a late reproductive age (range, 35–47 years) revealed that women with a BMI ≥ 30 kg/m² had 65% lower AMH levels than women with a BMI < 30 kg/m² (0.016 ng/mL vs. 0.046 ng/mL) [87]. For infertile women with diminished ovarian reserve (baseline serum FSH > 10 IU/L), women with a higher BMI (≥ 25 kg/m²) women had 33% lower serum AMH levels than normal BMI women [88]. A recent meta-analysis including 26 studies showed BMI is negatively correlated with AMH in the overall population [89].

Because of the altered hormonal metabolism in obese women, an inverse association of BMI and AMH has been described. However, the mechanism of obesity influencing AMH levels has not been fully elucidated [87].

6) BRCA mutations

Mutations of the *BRCA1* and *BRCA2* genes are known to contribute to the increased susceptibility to breast and ovarian cancers. The expression of *BRCA1* and *BRCA2* during human embryo development is known to affect embryogenesis, ovarian function, and female fertility [90]. Oktay et al. [91] reported that breast cancer patients with the *BRCA1* mutation had significantly poorer response to ovarian stimulation (≤ 4 retrieved oocytes) than non-carriers. These findings indicated that *BRCA* mutations can cause excess DNA damage in oocytes that would result in a smaller oocyte reserve and premature ovarian failure.

Various studies have also reported on the association between *BRCA* mutation status and serum AMH values. A cross-sectional study of women with a family history of breast cancer showed significantly low AMH levels in *BRCA1* mutation carriers but not in *BRCA2* mutation carriers [92]. In contrast, Johnson et al. [93] reported that carriers of the *BRCA2* mutation had more decreased AMH levels than non-carriers. Meanwhile, Michaelson-Cohen et al. [94] showed no significant differences in AMH levels between *BRCA1/2* mutation carriers and the general population. Given these various study results, more research is needed.

7) Vitamin D deficiency

Vitamin D is a steroid hormone that acts through the nuclear gene

transcription factor, and interest has increased in the role that vitamin D plays in female reproductive health. Merhi et al. [95] observed that women with insufficient and deficient levels of 25-hydroxyvitamin D (25OH-D) in follicular fluids (< 30 ng/mL) showed a two-fold increase in AMHRII messenger RNA (mRNA) expression levels compared to those with sufficient (≥ 30 ng/mL) 25OH-D levels. Vitamin D supplementation can counteract the repressive effect of AMH on granulosa cells and lead to follicular maturation. In a study of premenopausal women, 25OH-D and AMH levels exhibited seasonal variations in women with an 18% decrease in AMH levels in winter versus summer. They suggested that vitamin D supplementation prevented seasonal AMH changes [96]. In contrast, Pearce et al. [97] showed no correlation between serum AMH and vitamin D levels in PCOS or ovulatory women. Similarly, Drakopoulos et al. [98] reported that serum vitamin D levels had no association with ovarian reserve markers (AMH level, total AFC). Conflicting results from various clinical studies suggest the necessity for further research to reveal the actual effect of vitamin D on AMH levels.

4. Serum AMH level and PCOS diagnosis

As serum AMH level reflects excess small follicles not visible on ultrasonography, AMH level would theoretically be more accurate than the AFC [83,99,100], lending support to the notion that AMH may play a role in the diagnosis of PCOS. Given the strong implication of AMH in PCOS, AMH level could be used as a biomarker of the diagnosis of PCOS. Dewailly et al. [100] showed that a cutoff at 4.9 ng/mL had a high specificity of 97% and a better sensitivity of 92% than the AFC to distinguish patients with PCOS from normal women. A recent meta-analysis indicated that the cutoff value of 4.7 ng/mL had a sensitivity of 82.8% and a specificity of 79.4% for PCOS diagnosis, with an AUC of 0.87 [101]. However, there is currently no universal and consensual diagnostic threshold for serum AMH in the diagnosis of PCOS. The new European Society of Human Reproduction and Embryology guidelines, published in 2018, do not recommend the use of serum AMH levels as an alternative for detecting polycystic ovarian morphology (PCOM) or as a single test result for the diagnosis of PCOS [102].

In the future, with improved standardization of assays and established cut-off values based on large-scale validation in populations of different ethnicities and ages, AMH may be used as a precise diagnostic tool for PCOS or PCOM [101-103].

5. Opinions on the use of AMH level as a “fertility test”

Because of the convenience of sampling regardless of menstrual cycle and known age-specific values, AMH is now preferred as a biomarker to evaluate ovarian reserve in women. Serum AMH measurement is being considered a screening tool for women who want to

preserve their fertility in some clinical situations. However, the usefulness of AMH as a “fertility test” is not well known. Recently, Steiner et al. [104] determined the extent to which biomarkers of ovarian reserve are associated with reproductive potential among late reproductive-age women (age, 33–44 years). They concluded that women with low AMH levels (< 0.7 ng/mL) did not have a significant difference in predicted probability of conception by 12 attempted cycles compared to women with normal AMH levels. They also found that, among women without a history of infertility who attempted to conceive for less than 3 months, biomarkers that reflected diminished ovarian reserve were not associated with decreased fertility. On the other hand, Koo et al. [105] evaluated the association between serum AMH level and pregnancy rate and time to pregnancy after timed intercourse in 202 infertile women younger than 35. The pregnancy rate after timed intercourse was not significantly different between normal AMH and low AMH groups (< 2.5 ng/mL for women ≤ 31 years and < 2.0 ng/mL for women 32–34 years). However, the time to pregnancy was longer in the very low AMH group (< 1.19 ng/mL for women ≤ 31 years and < 0.6 ng/mL for women 32–34 years) than in the normal AMH group with statistical significance.

These inconsistent findings imply that using AMH levels to assess natural fertility for women without a history of infertility or subfertility may be inappropriate, even in late reproductive-age women. There is consensus of AMH as a good marker of ovarian reserve, but there is no current agreement on its use as a fertility screening test in fertile women.

Conclusion

Measuring serum AMH to predict an ovarian response to stimulation in ART, menopausal onset, and iatrogenic amenorrhea may be useful; thus, it must be added to individualized patient counseling. Given the strong implication of AMH in the pathophysiology of PCOS, AMH may be a biomarker of PCOS diagnosis in the future. It could be considered a screening parameter in selected populations of women for assisting with their reproductive life planning. However, agreement on its use as a screening tool in fertile populations is lacking. In the future, an international consensus on the screening of ovarian reserve in general populations of reproductive-age women is expected.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, & Project administration: YJC. Visualization: SRO. Writing - original draft: SRO. Writing - review & editing: SYC.

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