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REVIEW ARTICLE

Role of Anti-Müllerian Hormone in Gynecology: A Review of Literature

[1]Naina Kumar, [2]Amit Kant Singh

ABSTRACT

Anti-Müllerian hormone (AMH) or Müllerian inhibiting substance (MIS), is a dimeric protein part of the transforming growth factor (TGF)-beta subfamily. It plays two important roles in follicle genesis. First, it delays entrance of primordial follicle into pool of follicles in growth and secondly, it decreases the sensitivity of ovarian follicle toward follicle-stimulating hormone (FSH). The ovary-specific expression pattern in granulosa cells of growing non-selected follicles makes AMH an ideal marker for size of the ovarian follicle pool. This review summarizes recent literature concerning AMH and its role in various gynecological conditions.

Methods: The literature regarding AMH was searched from various English language journals and published peer-reviewed articles on PubMed, MEDLINE and Google Scholar till 2014.

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INTRODUCTION

Anti-Müllerian hormone (AMH), homodimeric glycoprotein consisting of two subunits, with total weight 140 kDa[1] belongs to TGF-β sub-family, which includes inhibin, activin, growth differentiation factor.[1] Gene encoding AMH is on short arm of chromosome 19.[2] Action is exerted through two transmembrane receptors: type I (AMHRI), type II receptor (AMHRII)[3] on target organs (gonads, Müllerian ducts).[4] Once activated, AMHRI phosphorylates receptor-regulated Smads. Smad complex accumulates in nucleus, regulates target gene expression.[5]

[1]Assistant Professor, [2]Associate Professor

[1]Department of Obstetrics and Gynecology, Mahatma Gandhi Institute of Medical Sciences, Wardha, Maharashtra, India

[2]Department of Physiology, Rural Institute of Medical Sciences Safai, Uttar Pradesh, India

Corresponding Author: Naina Kumar, Assistant Professor Department of Obstetrics and Gynecology, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, Maharashtra India, Phone: 9552515600, e-mail: drnainakumar@gmail.com

Anti-Müllerian hormone is not secreted in female embryo, allowing female sexual organ development.[6] Until recently, AMH was known for differentiation of male sexual characteristics.[7,8] Now, its role in females is gaining interest.

ANTI-MÜLLERIAN HORMONE: PRODUCTION, ACTION AND LEVELS

Anti-Müllerian hormone is produced by granulosa cells of follicles from the time at which follicle growth is initiated[9,10] and is a regulator of early follicular recruitment from the primordial pool.[11] Its expression continues until follicles reach approximately 8 mm in diameter, and is very low in larger antral follicles.[12,13] Consequently, there is a good correlation between AMH and antral follicle count (AFC).[14-19] In female neonates, AMH remains undetectable but increases gradually until puberty, and thereafter remains relatively stable throughout the reproductive period[20,21] and also in-between cycles in same woman.[22] Recent literature shows that there are fluctuations throughout the cycle (with lower levels during the early secretory phase) or even in-between consecutive cycles.[23] Still, these fluctuations are not considered clinically significant to recommend measurement of AMH at a specific phase of the menstrual cycle.[23]

To date, no single study has examined AMH across the lifespan in healthy females. Expression of the hormone in women is different at various stages of life, and starts to be detected at 36 weeks of gestation.[6,9,12,17,24] Its concentration reaches a maximum during puberty,[8] begins to decrease in adulthood, and disappears completely following the menopause.[25] Following a small decline in first 2 years of life, AMH levels gradually increase to peak at (mean 5 ng/ml) around age of 24 years.[26,27] In line with the pattern of oocyte loss, serum hormone levels gradually decline with increasing age and become undetectable around 5 years prior to menopause.[26,27] This suggests that AMH concentrations at any given age in both childhood and adulthood may mirror primordial follicular recruitment rates, rather than simply primordial follicle number.[26] Consequently across the female lifespan, circulating AMH will potentially exhibit an initial increase followed by a non-linear decline as is well established for the primordial follicle pool.[26,28,29] Hence, AMH concentrations decline with age.[18,30] The data for AMH concentrations in children is presently

Table 1: Range of anti-Müllerian hormone[33,34]

Interpretation	*AMH blood level (ng/ml)*
High (often PCOS)	Over 3.0
Normal	Over 1.0
Low normal range	0.7–0.9
Low	0.3–0.6
Very low	Less than 0.3

Note: 1 ng/ml = 7.14 pmol/L

limited.[31,32] The range of anti-Müllerian hormone is depicted in Table 1.

PHYSIOLOGY OF ANTI-MÜLLERIAN HORMONE

Functional roles of AMH in ovarian folliculogenesis were revealed by analysis of the follicle pool in ovaries of AMH-deficient mice at various ages.[35] The AMH null mice demonstrated accelerated depletion of primordial follicle number and an almost three-fold increase in smaller growing follicles.[11] Furthermore, this increase in number of growing follicles occurs despite lower serum FSH concentrations,[36] suggesting that in absence of AMH, follicles are more sensitive to FSH and progress through the early stages of follicular development.[26] In the mouse, AMH inhibited the effect of several growth factors known to have a stimulatory action on primordial follicle recruitment, such as Kit L and basic fibroblast growth factor.[37] In absence of AMH, ovaries contain more growing follicles, yet AMH-deficient mice have a normal ovulation rate.[35] Increased oocyte degeneration and follicular atresia suggests that AMH may also be a survival factor for small growing follicles.[38] The inhibitory effect of AMH on primordial to primary follicle transition was confirmed by *in vitro* studies of neonatal ovaries and ovarian cortical strips of various species, including human.[37,39-41] However, contradictory results using human ovarian cortical tissue have also been reported.[42] Several studies have shown that AMH expression remains high until follicle reaches a diameter of around 8 mm.[12,13,43,44] The intrafollicular concentrations of AMH in normal human antral follicles show a gradual reduction as the diameter of the follicle increases, and a sharp decline is observed at around 8 mm.[45] The rapid decline in AMH expression corresponds with the selection of dominant follicle, which is characterized by a transition from a low-estrogen producing state to one of rapidly increasing estrogen production.[35] E2 is instrumental in this decline through E2 receptor b, which interacts with the AMH promoter region.[46]

ASSESSMENT OF AMH SERUM LEVELS

Anti-Müllerian hormone is produced as a precursor protein, consisting of 70 kDa disulphide-linked monomers.[47] Proteolysis yields a 55 kDa N-terminal pro-region and a 12.5 kDa C-terminal mature region.[48,49] The pro- and mature homodimers remain noncovalently associated, resulting in a 140 kDa complex in circulation.[50] The mature region of AMH holds the biological activity of the protein but in contrast to other TGF-β family members, requires the N-terminal pro-region to obtain its full activity.[51] It has been suggested that the pro-region is involved in protein stability and folding.[52] The importance of assessment of serum AMH levels in females followed the insight that serum AMH might be a proxy for the size of the primordial follicle pool.[53] This led to the development of an AMH Enzyme-linked immunosorbent assay in 1990 and was recognized as a significant step in the assessment of ovarian reserve.[54-56] Later, Diagnostic Systems Ltd (DSL) and Immunotech, Beckman Coulter Ltd (IOT) introduced two commercial immunoassays for routine clinical assessment of ovarian reserve, known as 'first generation AMH assays'.[27] These assays employed two different antibodies against AMH and used different standards for calibration providing non-comparable measurements.[27] In this assay, a pair of highly specific monoclonal antibodies recognize epitopes in both the pro-region (F2B/7A) and mature regions (F2B/12H).[57] This assay, therefore, measures total AMH with a detection limit of 6.3 pg/ml.[57] Later on, it was found that Gen I assays gave variable AMH results due to storage and freeze-thaw instability. Assays using one or both antibodies directed against the pro-region are likely to exhibit this instability and careful attention to sample collection and storage may be required if reliable results are to be obtained from these assays.[58] Later, the manufacturer of IOT assay (Beckmann Coulter Ltd) consolidated the manufacturer of the DSL assay (Diagnostic Systems Laboratories Inc) and introduced a new assay 'Gen II AMH assay'. AMH Gen II assay was developed using the antibodies derived from first generation DSL assay and calibrated using standards used for IOT assay and was believed to be considerably more stable compared to the first generation immunoassays providing more reliable measurements.[27,59] This was verified by a multicenter study which showed that there was good agreement between these assays; the AMH Gen II assay giving values approximately 40% higher than the DSL assay.[60] Consequently, it was recommended that AMH results obtained using the DSL assay should be multiplied by a conversion factor of 1.4 in order to obtain the equivalent value in the Gen II assay. The Gen II assay was calibrated to the IOT AMH ELISA, yielding a sensitivity of 0.08 ng/ml.[59] Moreover, the AMH Gen II uses a pair of monoclonal antibodies directed to epitopes in the mature region of AMH[61] and correspondingly the AMH measured by this

assay is less affected by proteolysis. In addition, it can be used to measure AMH in monkey, bovine and other mammalian species, other than humans.[58]

FACTORS AFFECTING ANTI-MÜLLERIAN HORMONE LEVELS

Inter-individual variability of AMH is high, mainly due to high variability in the number of antral follicles within groups of subjects of similar age.[62-64] There is also ethnic variation, with African-American[65,66] and Hispanic[65] women having lower serum AMH levels than those found in Caucasian women, indicating discrepancy between ovarian follicle number and AMH production.[67] Some studies have indicated a negative relationship between BMI and AMH[68,69] but this has not been consistent.[70-74] In a recent study, AMH was negatively related to BMI but the relationship was age-dependent[72,73] suggesting that this is secondary to the stronger relationship of AMH and BMI with age. Similarly, contradictory results have also been reported on the relationship between smoking and AMH,[35] with some studies reporting reduced AMH levels in smokers[68,75,76] and others reporting similar values.[14,72,73,77,78] In a study, serum AMH levels on day 2, 3 and 4 of the menstrual cycles in women aged 38 to 50 years was measured and it was found that active smoking is associated with decreased serum AMH in late reproductive age and perimenopausal women confirming the effect of smoking on the depletion of antral follicles.[75]

The data concerning the impact of oral contraceptives on AMH values are divergent.[79] It has been suggested that AMH concentrations are not influenced by oral contraception,[80] but this finding has not been confirmed.[81] Contraceptives containing 0.035 mg of ethynyl estradiol and 2 mg of cyproterone acetate cause a significant suppression of gonadotropins and testosterone levels, a reduction in the number of ovarian small follicles[79] as well as a significant reduction in AMH levels.[81] On the other hand, gonadotropin-releasing hormone (GnRH) agonists do not seem to affect AMH concentrations.[82,83] This makes serum AMH an ideal marker for ovarian reserve. Several other factors affecting serum AMH levels include alcohol use and race.[14,82,84]

ANTI-MÜLLERIAN HORMONE AND OVARIAN RESERVE

Ovarian reserve usually refers to 'total number of remaining oocytes in the ovaries, which consists of number of resting primordial follicles and growing primary, preantral and antral follicles'.[85] To date, AMH has developed into a factor with a wide array of clinical applications,[35] mainly based on its ability to represent the number of antral and pre-antral follicles present in ovaries.[86] Release of AMH from the granulosa cells of antral follicles leads to measurable serum levels, and these concentrations have shown to be proportional to the number of developing follicles in the ovaries.[35] Therefore, AMH was considered to be a marker for the process of ovarian aging.[57] Recent studies support the hypothesis that serum levels of AMH can reflect the state of the ovarian follicles better (given its relative stability during the entire cycle) than the more usual hormonal markers [FSH, luteinizing hormone (LH), estradiol, and inhibin B], and hence appears to be a favorable candidate as a marker of the ovarian reservoir.[4,8,87]

Moreover, since AMH levels are not affected by changes such as pregnancy, GnRH agonist treatment, or oral contraceptive pills administration, measurement of AMH seems to be an ideal test for ovarian reserve which can be assessed at any point during the menstrual cycle.[82,88-92] Also serum AMH appears to be solely of ovarian origin, as it was undetectable in women 3 to 5 days after bilateral oophorectomy.[88,89] Hence, reduction in the number of preantral and antral follicles will result in serum AMH reduction. In the last few years, many authors have been able to confirm the strong association between serum AMH and the ovarian pool.[4,25,88-90,93-96]

ROLE OF ANTI-MÜLLERIAN HORMONE IN POLYCYSTIC OVARIAN SYNDROME

Women with PCOS show markedly raised AMH levels, with a 2 to 4-fold higher[17,97-99] levels than in healthy women, both due to increased number of small antral follicles and intrinsic characteristics of granulosa cells, ultimately resulting into anovulation.[35] However, when production of AMH per granulosa cell was compared between normal ovaries, ovulatory and anovulatory PCOS,[100] AMH production was on average 75 times higher per granulosa cell from anovulatory PCOS and 20 times higher from ovulatory PCOS than healthy ovaries.[100] Similarly, concentrations of AMH were found to be five times higher in follicular fluid from unstimulated follicles from women with anovulatory PCOS compared to women who were ovulatory.[101] Interestingly, follicle number only added 5.3% to the variance in the concentration of AMH.[102] This indicates that increase in AMH is due to an intrinsic property of granulosa cells in PCOS, a property that persists even after stimulation for *in vitro* fertilization.[103] The cause of such high levels of AMH in antral follicles in PCOS is currently unknown. However, there is evidence to support, role for androgens as a positive correlation with AMH in serum[17,97,104,105] and over-production of androgens is an intrinsic defect of theca cells from PCOS.[106] Another candidate for the cause of the increase in AMH in PCOS is insulin. Hyperinsulinemia is known to

affect anovulatory women more than ovulatory women,[107] and falling insulin concentrations do correlate with the return of ovulatory cycles.[108] Another study also reported a direct correlation between AMH and insulin insensitivity.[109] Insulin has been shown to enhance gonadotropin-stimulated steroid production in GCs and theca;[110] therefore, the raised AMH concentrations may be secondary to an effect of insulin on androgen levels. However, some other studies have failed to find a direct correlation between insulin and AMH concentrations,[97,104] and found that even when insulin levels have reduced with treatment, a fall in serum AMH has not followed directly.[105,111]

Ideally, AMH should be lower in preantral follicles, and then higher once the follicle reaches the antral stage, however, prenatal testosterone treatment of sheep produced precisely this effect.[112] Anti-Müllerian hormone significantly decreases FSH and LH induced aromatase expression in granulosa cells as well as reducing the activity of ovary-specific aromatase promoter II, resulting in a significant reduction in E2 production.[113] Anti-Müllerian hormone also inhibits FSH-stimulated FSH receptor mRNA expression.[113] The fact that AMH is inhibitory to factors required for follicle growth adds considerable significance to the finding of high AMH in PCOS. Luteinizing hormone reduces AMHRII expression in granulosa luteal cells collected from women with normal ovaries and ovulatory PCOS, but was unable to do so in women with anovulatory PCOS.[114] It can be envisaged that AMH content in antral follicles in these ovaries would be sufficient to inhibit FSH-stimulated aromatase expression and would thus prevent the inhibitory effect of E2 on AMH production.[113] Hence, the value of AMH in the diagnosis of PCOS remains controversial but it may replace AFC in the future. In addition, the serum AMH correlates with the severity of PCOS and precisely with the severity of both hyperandrogenism[115] and oligo-anovulation.[17,116]

Anti-Müllerian hormone concentrations in women with PCOS were independently and positively correlated with testosterone, androstendione and free androgen index (FAI) values.[17,97] It is known that AMH levels decrease with age in women with normal ovulatory cycles.[79] A similar decline is observed in women with PCOS but at a slower reduction rate.[117] This could be interpreted as indicating that ovarian aging is slowed down in women with PCOS, possibly due to the negative effect of AMH on the recruitment of primordial follicles.[79] High AMH levels were observed in adolescent girls, aged 12 to 18 years, with PCOS compared to controls.[118] Furthermore, increased AMH concentrations have been found in girls aged 4 to 7 years born of mothers with PCOS.[119] Evidence that hereditary factors contribute to the pathogenesis of the syndrome is also found in animal studies showing that prenatal exposure to increased androgen levels can lead to offspring with PCOS features.[120,121] Anti-Müllerian hormone levels were lower in overweight and obese women with PCOS than in normal-weight women with the syndrome and healthy controls.[115] Other studies have also confirmed this finding.[17,100] Furthermore, an independent positive correlation between AMH and LH levels has also been found.[122] Previews research has also shown that normal-weight women with PCOS presented higher LH values than overweight and obese women with the syndrome.[123] Thus, the lower LH concentrations observed in obese women may be attributed to the increased aromatization of androgens to estrogens which takes place in the peripheral fat tissue, resulting in the suppression of LH.[124] Hence, higher AMH levels seen in normal-weight women with PCOS compared to obese women with the syndrome could be attributed to the higher LH levels.[79] Therefore, AMH levels have higher specificity and sensitivity (92 and 67%, respectively) as a diagnostic marker for PCOS.[125]

ROLE OF AMH IN *IN VITRO* FERTILIZATION (IVF)

Recent data shows a strong and positive correlation between basal AMH serum levels and number of retrieved oocytes in women undergoing controlled ovarian hyperstimulation (COH).[126] Studies have shown that AMH measurement is the best prognostic marker of the ovarian response to controlled ovarian stimulation during IVF cycles, especially when a single marker is determined.[25,61] Serum AMH levels are more strongly related to ovarian follicular status than serum inhibin B, estradiol, FSH and LH on cycle day 3.[16] A study revealed that AMH concentrations present a negative linear correlation with basal FSH levels in women having poor response to COH with human gonadotropins.[126] Specifically, AMH concentrations of 1 ng/ml correspond to FSH values of 10 IU/L, whereas 0.5 ng/ml of AMH corresponds to 15 IU/L.[79] However, in conditions with high LH and normal or low FSH levels, as in PCOS, AMH concentrations are positively correlated with LH concentrations, while they are not negatively correlated with FSH.[127] Anti-Müllerian hormone levels have prognostic value for both the number of oocytes retrieved during follicular aspiration and the number of arrested cycles.[61] Compared to antral follicle count, AMH concentrations could reliably and equally predict poor response to ovarian stimulation in IVF cycles.[127] Recently, it was reported that AMH levels could also recognize women prone to develop ovarian hyperstimulation syndrome (OHSS) during multiple ovulation induction with human gonadotropins.[128] In a prospective study, it was found that the live birth rate,

following IVF, was increased when AMH levels were high prior to ovulation induction with human gonadotropins.[128] This could be attributed to the greater number of oocytes retrieved by women with high AMH levels, given that high basal AMH concentrations indicate a great number of selectable follicles. On the other hand, the results of a large meta-analysis showed that AMH levels are very poor predictors of pregnancy outcome.[129]

An alternative approach could be the evaluation of AMH levels in the follicular fluid.[74] Studies reveal[130,131] that AMH follicular fluid levels were strongly associated with pregnancy rates in IVF cycles. Toner et al suggested the following general guidelines.[132]

- Anti-Müllerian hormone < 0.5 ng/ml predicts reduced ovarian reserve with less than three follicles in an IVF cycle.
- Anti-Müllerian hormone < 1.0 ng/ml predicts baseline ovarian reserve with a likelihood of limited eggs at retrieval.
- Anti-Müllerian hormone > 1.0 ng/ml but < 3.5 ng/ml suggests a good response to stimulation.
- Anti-Müllerian hormone > 3.5 ng/ml predicts a vigorous response to ovarian stimulation and caution should be exercised in order to avoid ovarian hyperstimulation syndrome.

Furthermore, studies have demonstrated that follicular fluid AMH level has positive correlation with fertilization and embryo quality.[130-133] A study done in patients who had undergone IVF demonstrated that the follicular fluid AMH levels in fertilized group was higher that in non-fertilized group.[134] Similar positive relationship between follicular fluid AMH and embryo quality in women undergoing IVF was demonstrated by another study also.[135] Hence, AMH appears to be a novel predictor of response to IVF cycles.

ROLE OF ANTI-MÜLLERIAN HORMONE IN OTHER GYNECOLOGICAL CONDITIONS

Serum AMH is a good marker of tumors originating from granulosa cells. Indeed, AMH levels are found increased in 76 to 93% of women with granulosa cell tumors.[136] Moreover, elevation of AMH levels precedes the tumor clinical recurrence by up to 16 months.[137] Consequently, AMH could be used as an early diagnostic marker as well as a marker of granulosa cell tumor recurrence. Along with inhibin its determination was successfully tested as a marker of early diagnosis and response to the treatment. Anti-Müllerian hormone appeared to be more specific, while sensitivity of both hormones was comparable.[138] The values of AMH in these patients correlated well with the size of the tumor.[139] Recent research brought evidence that AMH determination may serve as a tool for diagnosis of some other neoplasia, as for instance a prostate cancer and could be used for detection of tumor recurrence. The results, however, were not definite.[140]

Anti-Müllerian hormone can be used to access ovarian function after chemotherapy and radiotherapy in young women. This was first described by a study which reported fall in AMH concentrations in women who had had childhood cancer but who still had regular menses, compared with an age-matched control group,[141] whereas no difference in serum FSH or inhibin B was reported between groups. Similar findings have been shown in breast cancer survivors.[142] Another study of ovarian function in young adults following treatment for childhood Hodgkin's lymphoma demonstrated a clear cut dose related fall in AMH concentration in relation to number of chemotherapy cycles.[143] Follicle-stimulating hormone also rose with increasing treatment, but AMH appeared to have greater sensitivity to detect ovarian damage at lower doses of chemotherapy. The gonadotoxicity of alkylating agent-based protocols has been shown in a range of childhood and adult malignancies,[144-146] but is most clearly demonstrated in a prospective study in young women with lymphoma.[147] Moreover, in a prospective analysis of girls with varied diagnosis (and therefore undergoing differed therapies) at different ages, AMH declined during repeated chemotherapy cycles.[148] Similarly, radiotherapy is also widely recognized to cause ovarian damage even at low doses and women treated with radiotherapy that includes the pelvis (including abdominal pelvic therapy in children or total body irradiation) generally have very low or undetectable AMH concentrations.[145,146]

Anti-Müllerian hormone can also be used for the study of impact of ovarian surgery on the ovarian reserve. This was demonstrated by two systematic reviews which studied the impact of ovarian surgery for endometriosis on AMH.[149] Both concluded that ovarian endometrioma surgery is associated with a decline in serum AMH, indicating the removal of a significant part of the ovarian reserve.[149] Further, a large retrospective analysis has confirmed the impact of endometrioma surgery on the ovarian reserve as detected by serum AMH.[150] The emerging data on relation between AMH level at a certain age and the timing of menopause has set a scene for an individualized prediction of reproductive lifespan, and from there potential prevention of infertility based on early ovarian aging.[35] Several studies have suggested that a single AMH measurement may be a good predictor of the onset of menopause in aging women.[96,151] Recent studies have added serum AMH as a marker for menopausal, staging because it declines much earlier than other signs of menopause, such as increasing serum

FSH or irregular menses.[152] Furthermore, it was shown to improve the prediction of menopause onset more than maternal age.[153] Interestingly, a recent study in 44 Japanese women demonstrated that menopause onset was within 3 years after AMH became undetectable,[154] instead of 5 years shown by a study of large US and European populations.[155]

CONCLUSION

The current review suggested that AMH is a potent marker of ovarian reserve. It can also be used for diagnosis of various gynecological conditions, like granulosa cell tumor, PCOS, menopausal state, artificial reproductive techniques. Hence, AMH has emerged as an effective tool for detection of various gynecological conditions and that too with high sensitivity and specificity.

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