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Review Article

Anti-Müllerian hormone in health and disease: a review

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ABSTRACT

Anti-Müllerian hormone (AMH) is a homodimeric glycoprotein, member of the transforming growth factor β family of growth and differentiation factors. In the ovary, AMH has an inhibitory effect on primordial follicle recruitment as well as on the responsiveness of growing follicles to follicle-stimulating hormone (FSH). The ovary-specific expression pattern in granulosa cells of growing non-selected follicles makes AMH an ideal marker for the size of the ovarian follicle pool. AMH levels accurately reflect the ovarian follicular reserve and could, therefore, be considered as an extremely sensitive marker of ovarian aging and a valuable tool in the diagnosis and the recognition of recurrence of granulosa cell tumors. Furthermore, AMH could be a surrogate diagnostic marker of polycystic ovary syndrome in cases in which ultrasonographic examination is not possible. Additionally AMH evaluation is of clinical importance in predicting the success of in vitro fertilization (IVF). Special reference is made to the possible implications of AMH in the pathogenesis of polycystic ovary syndrome and the relationship between AMH and obesity. AMH also plays important role in evaluation of infants with ambiguous genitalia and other intersex conditions. This article is a review of the clinical usefulness of AMH evaluation in the fields of gynecological endocrinology, menopause, gynecological oncology and assisted reproduction and also in pediatric patients.

Keywords: Anti-Müllerian hormone, Ovarian aging, Polycystic ovary syndrome, Obesity, Assisted reproduction, Tumor marker

INTRODUCTION

Anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance (MIS), is a homodimeric glycoprotein linked by disulfide bonds and a molecular weight of 140kDa.[1] The hormone belongs to the transforming growth Factor-β (TGF-β) super family which includes more than 35 structurally related peptides, including activins, inhibins, bone morphogenic proteins (BMPs) and growth differentiation factors.

Many of these are involved in the reproductive function of both the sexes.[2] The gene encoding AMH is located in the short arm of chromosome 19 Band 19p 13.3 in humans. The AMH gene is 2750 bps long and it is divided into five exons.[3] AMH action is exerted through two receptors: type I receptor (AMHRI) and type II receptor (AMHRII) which are present on the AMH target-organs (gonads and Müllerıan ducts) AMHR2 to signal through a BMP-like pathway, by recruiting one of the type I receptors; ALK 2, 3 or 6. Once AMH binds to AMHR2, the type I receptor becomes recruited, thus forming a receptor complex.

Activation of the type I receptor causes the phosphorylation of the R-Smads. These proteins bind to the common SMAD4 protein, resulting in the translocation of the complex into the nucleus and its binding directly to the DNA to regulate gene expression or interacting with other DNA-binding proteins. AMH was originally identified because of its fundamental rolein male sex differentiation. Indeed, expressed in the Sertoli cells of fetal testis, AMH induces the regression of the Mullerianducts.[4] In the absence of AMH, Mullerian ducts evolved into uterus, fallopian tubes and the upper part of the vagina. In women AMH is produced by granulosa cells, from pre-antral and antral follicles and the main physiological role of AMH in the ovary seems to be limited to the inhibition of the early stages of follicular development.[5]

Physiology of AMH

In the male fetus it is expressed in the Sertoli cells of the testes, which leads to Müllerian regression. In women, AMH is produced by the Granulosa Cells (GC) of follicles. Specifically, GC produces AMH from the stage of the primary follicle to the initial formation of the antrum.[6] In female neonates, AMH is virtually undetectable but increases gradually until puberty and remains relatively stable thereafter and throughout the reproductive period.

AMH concentration remains stable throughout the menstrual cycle. Recent data, however, have shown that there are fluctuations throughout the cycle (with lower levels during the early secretory phase) or even between consecutive cycles. Nevertheless, these fluctuations are not considered clinically significant to recommend the measurement of AMH concentrations at a specific phase of the menstrual cycle.[7] Women of 25 years of age had higher serum AMH concentrations than those aged 35 years and above, and when women were followed longitudinally for a period of between 1 and 7 years, there was a decrease in serum AMH levels, with levels becoming undetectable when menopause was reached.

Expression of AMH in the ovary

Ovarian AMH has been reported to be produced from 36 weeks of gestation in the GCs and to be expressed until menopause.[6] During folliculogenesis, two regulatory selection processes can be recognized. These regulatory steps both involve the recruitment of follicles. During the first selection, known as initial recruitment, follicles are recruited from the dormant primordial follicle pool. During the second selection, known as cyclic recruitment, growing follicles are selected to grow until the preovulatory stage.

This second selection is the result of the rise of FSH levels during each reproductive cycle. Only those large preantral and small antral follicles, which are sensitive enough to FSH, will be rescued from atresia. AMH inhibits recruitment of primordial follicles declining in dominant follicles and with equivocal expression in atretic follicles, corpus luteum and primordial follicles. AMH is thus a good indicator of the size of the ovarian antral follicle pool. AMH decreases the sensitivity of large preantral and small antral follicles to FSH.[8,9] Most of the evidence regarding AMH actions has come from animal studies. Durlinger et al, showed that AMH knock-out mice had three times more small non-atretic growing follicles and a reduced number of primordial follicles compared with wild mice.[9]

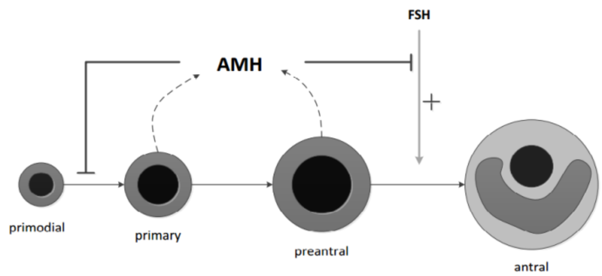

Figure 1: Model of AMH action in the ovary.

Progressing stages of folliculogenesis. AMH is produced by the small growing (primary and preantral) follicles in the postnatal ovary and has two sites of action by inhibiting initial follicle recruitment. And by inhibiting FSH-dependent growth and selection of preantral and small antral follicles (Figure 1).[10]

AMH as a marker for ovarian aging and responsiveness- a reliable marker of ovarian function

It is well known and found that reproductive capacity is closely but variably related to chronological age and is dictated by biological ovarian age or ovarian reserve. The number of primordial follicles decreases with age and is virtually depleted at menopause. Reduced ovarian reserve results from a decline in the ovarian pool of follicles. A marker of ovarian reserve which would reliably predict reproductive capacity and the time of onset of menopause would be a significant clinical tool with which to assist women to plan childbearing.

AMH is one such biomarker. There is a very good correlation between the serum AMH level and the number of follicles potentially capable of maturation and thus also the ovarian functional reserve.[3] AMH levels and follicle number with age has been widely accepted. AMH shows non-significant intra-cycle and inter-cyclevariation during menstrual cycle.[11] This is an important advantage of AMH over FSH, as it can be reliably measured at any stage of the menstrual cycle.

AMH levels remain unchanged in the first trimester of pregnancy, but show a decline in the second and third trimesters, with a return to pre-pregnancy levels early in the puerperium. The levels during pregnancy, however, do not become undetectable, indicating that follicular development is not completely abolished.[12] There is also a non-significant variation in AMH levels during short-term oral contraceptive use and short-term gonadotrophin- releasing hormone analogue administration. Long-term use (for more than 1 year) of oral contraceptives and gonadotrophin releasing hormone analogues can reversibly reduce AMH concentrations. These studies confirm the presence of continuous ovarian activity independent of FSH stimulation.[13]

Thus, AMH could be used as a marker of ovarian aging given that the reduction in hormone levels reflects the age-dependent fall in the follicular potential of the ovary. Indeed, AMH values have greater sensitivity than inhibin B, FSH and estradiol values in predicting ovarian follicular reserve.

AMH and polycystic ovary disease (PCOD)

AMH besides being a marker for a diminishing follicle pool, serum AMH level can also serve as a marker in ovarian pathophysiology, such as polycystic ovary syndrome (PCOS), in which the antral follicle pool is enlarged. PCOS is one of the most common endocrine disorders in women of reproductive age.[17]

PCOS encompasses a broad spectrum of clinical and biochemical characteristics, and, although the mechanisms leading to PCOS are still poorly understood, the common denominator is a disturbance in the selection of the dominant follicle resulting in anovulation. It is characterized by an ovulation manifested as oligo- or amenorrhea, elevated levels of circulating androgens, and polycystic ovaries as visualized by ultrasound. 50% of women with PCOS fulfil the criteria of metabolic syndrome and that PCOS is frequently associated with insulin resistance accompanied by compensatory hyper-insulinemia, resulting in an increased risk for the development of type 2 diabetes mellitus and cardiovascular risk.

The defective selection mechanism results in an accumulation of small antral follicles, which contribute significantly to the production of AMH.

Pigny et al indicated that serum AMH levels were three-fold higher in PCOS patients than in controls, and the elevated levels of AMH were significantly related to the follicle number in women with PCOS.[14] In PCOS, the follicular excess is mainly caused byan increase of small antral follicles upto 2-5mm in size. Raised AMH levels in PCOS were initially thought to be due only to greater antral follicle numbers, but studies have shown greater AMH production per granulose cell and per antral follicle.[15]

It has been suggested that aromatase activity in PCOS patients might be decreased because follicles from PCOS women do not produce large amounts of E2, and also contributes to the severity of PCOS.[16] AMH concentrations in women with PCOS were independently and positively correlated with testosterone, androstendione and free androgen index (FAI) values.[14] A substantial proportion of PCOS women are obese and exhibit insulin resistance and compensatory hyperinsulinemia, account for the hyperandrogenism, because insulin acts synergistically with LH to enhance androgen production by theca cells.[17] It is known that AMH levels decrease with age in women with normal ovulatory cycles.

A similar decline is observed in women with PCOS, but at a slower reduction rate. 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.[18] Oxidative stress has recently been implicated in the pathogenesis of the an ovulatory process. A direct relationship between PCOS, an ovulatory process and AGEs is supported by finding increased serum AGEs levels and increased expression of their receptors in macrophages (RAGE) as well as elevated deposition in ovarian tissues in PCOS women.[19]

Finally, AMH measurement has been found to offer a relatively high specificity and sensitivity (92 and 67%, respectively) as a diagnostic marker for PCOD.[14] On this basis it has been proposed that in situations where accurate ultrasound data are not available, AMH could be used instead of the follicle count as a diagnostic criterion for PCOS.

AMH and obesity

Obesity has been associated with reduced fertility, even in the presence of ovulatory menstrual cycles, and to increased probability of miscarriage compared with normal weight women.[20] Non-PCOS obese women show reduced levels of inhibin B and AMH suggesting that obesity may be associated with impaired ovarian reserve.[21] In a recent study, it was found that obese women of late reproductive age35-49 years had significantly lower AMH levels, (up to 65%), compared to normal-weight women of similar age. This inverse correlation between BMI and AMH levels has not been fully explained. Three hypotheses have been proposed:

- Obesity may affect the catabolism of AMH,
- Obesity could reduce the ovarian potential, and
- Obesity may be related to ovarian dysfunction.

Certainly, more studies are necessary to elucidate the impact of obesity on ovarian function. Therefore, 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. 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.[22]

AMH in assisted reproduction

The clinical significance of AMH determination was first proven in assisted reproduction medicine, as AMH serum levels reflect the ovarian reserve potential with high accuracy. 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.[23]

AMH levels have prognostic value for both the number of oocytes retrieved during follicular aspiration and the number of arrested cycles. Compared to antral follicle count, AMH concentrations could reliably and equally predict poor response to ovarian stimulationin IVF cycles. Recently, it was reported that AMH levels could recognize those women prone to express ovarian hyper stimulation syndrome (OHSS) during multiple ovulation induction with human gonadotropins.[23]

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. 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. An alternative approach could be the evaluation of AMH levels in the follicular fluid. Fanchin et al showed that AMH follicular fluid levels were strongly associated with pregnancy rates in IVF cycles, these findings also having been confirmed by other researchers.[24]

AMH levels measurement in oocyte donors were not decreased in women who underwent repetitive oocyte donation (three to six cycles), implying that ovarian aging is not advanced in oocyte donors.[23] The women with low AMH levels tended to get fewer eggs during IVF than the women with high AMH levels. Pregnancy rates were also lower in the women with low AMH levels. According to La Marca et al.[23] Cut-off values for AMH of 0.7-0.75 ng/ml have been proposed for the identification of poor responders by several groups.

Most importantly, the live birth rate for women with basal AMH, 0.7ng/ml is estimated to be 15% which may be considered highly acceptable for patients anticipated to be poor responders. Women with high AMH levels are considered to be at risk for hyper response and OHSS.[25] Hence these women should be informed about this risk. A low FSH starting dose followed by the use of GnRH antagonists have been shown to reduce the incidence of OHSS and may be proposed as a first line treatment for patients with high serum AMH levels. Moreover the use of GnRH antagonist permits the triggering of ovulation by means of GnRH agonist instead of hCG and this practice has been recognized as useful in the prevention of OHSS.[26]

AMH as a tumor marker

The fact that the expression of AMH is confined to GC of primary follicles up to the initial antral formation has rendered the evaluation of this hormone candidate marker for the diagnosis of ovarian tumors of GC origin. Indeed, AMH levels are found increased in 76-93% of women with GC tumors. Moreover, elevation of AMH levels precedes the tumor clinical recurrence by up to 16 months. Consequently, AMH could be used as an early diagnostic marker as well as a marker of GC tumor recurrence.[27]

AMH as a tumor inhibitor

Although the origin of ovarian epithelial tumors has widely been thought to originate from the coelomic epithelium that covers the ovarian surface, a new and well supported theory has placed their origin in tissues that embryo logically derive from Müllerian ducts. Recent data strongly indicate that a great number of tumors of ovarian origin arise from the fimbriated end of the fallopian tube as well as from components of the secondary Müllerian system.[28] AMH induces the regression of Müllerian ducts. Based on this fact some researchers hypothesized that AMH could be used in the treatment of ovarian epithelial tumors. Indeed, several studies showed that AMH inhibited epithelial ovarian cancer cells *in vitro*. Nevertheless further studies are required to definitively establish whether AMH has potential for clinical use in the treatment of these tumors.

AMH in male fertility-AMH in testicular physiology

AMH is the earliest sertoli cell specific protein expressed by the male gonad. It is secreted by the testis from the eighth week of pregnancy and remains secreted at high levels until puberty, when Sertoli cell maturation is characterized by a decreasing AMH production.[29] During puberal development AMH expression falls, coinciding with the increase in androgen secretion by Leydig cells.

The reduction in AMH levels at puberty is considered a clear marker of the elevation of intratesticular androgen concentration which inhibits sertoli cell. Paralleling the situation in women, the main physiological role of AMH in the adult male seems to be limited to the paracrine control of testicular function. AMH inhibits aromatase activity in sertoli cells and testosterone production by Leydig cells. Indeed, male mice that over-express AMH have lower levels of testosterone and Leydig cell hypoplasia and conversely, mice with null mutations in AMH or AMH RII have Leydig cell hyperplasia.[30]

As AMH is produced at high level before puberty its measurement can serve as a reliable marker for the presence of testicular tissue in childhood when levels of testosterone are very low. On this basis AMH is useful in the differential diagnosis of intersex conditions and disorders associated with androgen insensitivity.[31] Lee et al, found that AMH measurement is particularly helpful in patients with bilateral non-palpable gonads.[32]

In these patients normal AMH levels provide reassurance that the testis can be present but not descended. In the adult man, AMH is also present in seminal fluid at concentrations that may be significantly higher than those observed in serum.[33] The data comparing seminal and serum AMH concentrations in adults suggests that after puberty AMH is secreted preferentially by the apical pole of the sertoli cells toward the lumen of the seminiferous tubules resulting in higher concentrations of AMH in the seminal plasma than in the serum.

AMH measurement in infertile men

Appasamy et al, found as AMH is a specific marker of Sertoli cell function and is secreted in the serum and seminal fluid, its measurement in both the compartments may be useful in obtaining information on spermatogenesis, particularly in infertile men a correlation of serum AMH levels with sperm count and serum FSH levels has been reported.[34]

(Tu¨ttelmann et al, in his largest study to date, performed on 199 men, no significant differences were found in serum AMH levels between controls and men with oligozoospermia, confirming that serum AMH is not of diagnostic significance in men with impaired spermatogenesis.[35] (Muttukrishna et al, found that serums AMH levels have been found to be significantly lower in non-obstructive azoospermic (NOA) than in obstructive azoospermic (OA) patients and normal fertile men).[36] However, the wide overlapping of values between controls and infertile men prevents this hormone from being a useful diagnostic marker.

In males, the determination of AMH may be useful in the investigation of gonadal function, the differential diagnosis of intersexuality and cryptorchidism/anorchism and in the diagnosis of precocious/late puberty. AMH can be used to detect the presence of testes in cryptorchidic boys.[36]

Indication for AMH

AMH also enables: (1) prediction of both over and poor response in the controlled ovarian stimulation environment; (2) the most appropriate stimulation regimen to be determined; and (3) pre-treatment counseling helping couples make an appropriate and informed choices. Recent reports further suggest that AMH may be useful in the following situations, including prediction of long-term fertility, prediction of the age of menopause, prediction of ovarian ageing in women prior to or following chemotherapy, prediction of long-term fertility following ovarian surgery screening for polycystic ovaries.

Table 1: Reference range for female and male.[37]

Age	Unit	Female	Male
		Value	**Value**
Younger than 24 months	ng/mL	<5	15-500
	pmol/l	35	100-3500
24 months to 12 years	ng/mL	<10	7-240
	pmol/l	<70	50-1700
13-45 years	ng/mL	1 - 10	0.7-20
	pmol/l	7 - 70	5-140
More than 45 years	ng/mL	<1	-
	pmol/l	<7	-

CONCLUSION

AMH shows the potential to be a reliable marker of ovarian reserve and reproductive performance. AMH levels are strongly correlated with the size of the follicle pool, and because of the lack of cycle variations, serum levels of AMH are a good candidate for inclusion in standard diagnostic procedures to assess other ovarian dysfunctions, such as premature ovarian failure.

Knowledge of the serum AMH levels in such conditions might provide more insight into the possible cause or effect of altered AMH levels. It is a good predictor of poor response to fertility treatment, which can allows the individualization of stimulation regimens; it can also be used to alter the stimulation protocol in women with a high potential for developing OHSS.AMH levels reflect with high accuracy the ovarian follicle reserve, and this has been demonstrated innumerous studies. Therefore, AMH evaluation has great clinical importance in predicting the success of IVF cycles. AMH levels represent the most sensitive marker for the inevitable decline in the number of primordial follicles related to aging. Furthermore, AMH determination can be used in the diagnosis or the follow-up of women with tumors of granulosa cell origin. Additionally, AMH could be used as a supplementary marker of polycystic ovary syndrome in cases where the ultrasonographic examination of the ovaries is not feasible. Finally, the recently revealed relation between AMH and obesity will be a future research target in pathogenetic mechanisms linking obesity and gonadal dysfunction.

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