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## GYNECOLOGICAL UTILITY OF ANTI MULARIAN HORMONE IN FEMALE: A REVIEW

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### ABSTRACT

Anti-mullerian hormone (AMH), also known as mullerian inhibiting substance (MIS), discovered in 1947 by Alfred Jost. It is a dimeric glycoprotein member of TGF- $\beta$  superfamily. The AMH secretion starts from 36 weeks of pregnancy in preantral and early antral follicles smaller than 4 mm. In females, AMH is mainly secreted by the granulosa cells of ovarian early developing follicles; it reaches peak levels after puberty and steadily decreases until menopause. AMH levels are stable during the menstrual cycle. Until puberty, serum levels of AMH are negligible, but they increase thereafter to levels comparable with those in men, probably as a result of follicular growth, and they remain detectable until the end of ovarian activity. Normal values of AMH in the females are: 1-8  $\mu\text{g/l}$  in the fertile phase. Values below 1  $\mu\text{g/l}$  suggest reduce fertility and values below 0.025  $\mu\text{g/l}$  suggest infertile. Increase values of AMH correlate with the severity of the disease. The molecule has evolved in the last few decades for the assessment of ovarian reserve in females. AMH can be used as a screening test to assess the fertility status of women wishing to have children beyond 35 years of age. AMH levels are found increased in 76-93% of women with granulosa cell tumors.

**KEYWORD:** Anti-Mullerian Hormone (AMH), Infertility, Polycystic Ovarian Syndrome (PCOS), Anovulation, Premature ovarian failure.

### INTRODUCTION

Anti Mullerian Hormone (AMH) was reported for the first by A. Jost in 1940. The author described a protein substance formed in testes of mammals including man and different form of testosterone, responsible for regression of Mullerian duct. 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.<sup>[1]</sup> The hormone belongs to the Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) superfamily. The gene encoding AMH is located in the short arm of chromosome 19.<sup>[2]</sup> 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 Müllerian ducts).<sup>[3]</sup>

In male it is synthesized from Sertoli cells of testes since the 5th week of the embryonic development and during the whole life.<sup>[4]</sup> AMH plays an important role in male sex differentiation as AMH is produced by fetal Sertoli cells at the time of testicular differentiation, and induces regression of the Mullerian ducts. In the absence of AMH production or dysfunction of its receptors, the

Müllerian ducts develop into the oviducts, uterus, fallopian tubes and the upper third part of the vagina in genetic male embryos.<sup>[5, 8]</sup>

### Physiology of Anti -Mullerian hormone (AMH) in Females

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. In female neonates, AMH is virtually undetectable but increases gradually until puberty and remains relatively stable thereafter and throughout the reproductive period.<sup>[6, 7]</sup>

In the ovaries of female fetuses, AMH expression has been observed as early as 32 weeks gestation in humans.<sup>[9]</sup> AMH continues to be expressed in the growing follicles in the ovary until they have reached the size and differentiation state at which they may be selected for dominance. In the mouse this occurs at the early antral stage in small growing follicles,<sup>[10]</sup> whereas in the human it is evident in antral follicles 4–6 mm in diameter.<sup>[11]</sup> Thus, AMH is expressed in follicles that have undergone recruitment from the primordial follicle

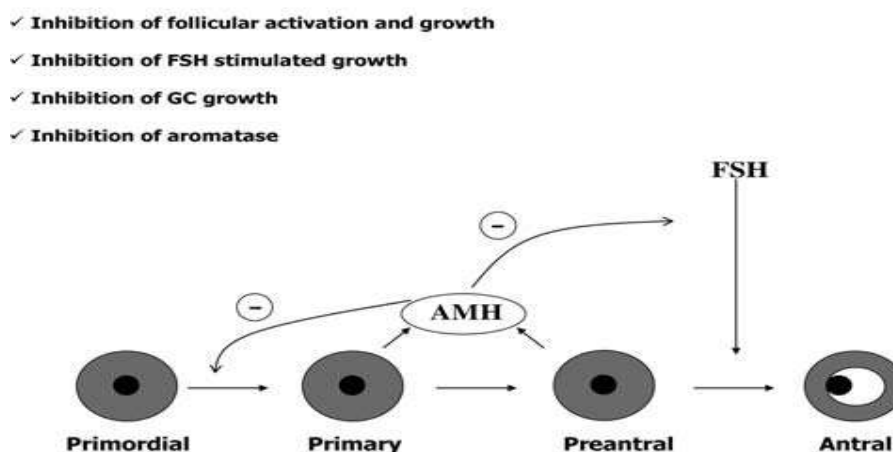
pool but have not been selected for dominance. AMH is not expressed in atretic follicles or theca cells.<sup>[12, 8, 13]</sup>

### AMH in ovarian development

AMH is specifically expressed in granulosa cells of small growing follicles. AMH has also been suggested to exert a physiological effect on antral follicles in the human ovary before final selection. There exists a fine-

tuned and delicate balance between estradiol (E2) (and inhibin) output by the preovulatory follicle and gonadotropin secretion by the pituitary to ensure that ovulation is triggered exactly at the right time.<sup>[14]</sup> Recently, it has been suggested that AMH may exert a physiological role in down-regulating the aromatizing capacity of granulosa cells until the time of follicular selection.<sup>[15]</sup>

### Possible actions of AMH in the ovary



[Figure 1: In women, AMH expression can first be observed in primary follicles, and is strongest in pre-antral and small antral follicles. AMH may play an inhibiting role in initial recruitment and in the selection of the dominant follicle.]<sup>[16]</sup>

**AMH:** Anti-Mullerian hormone; GC: Granulosa cell.

### AMH in follicular development

In follicular fluid, the highest concentrations of AMH are found in small antral follicles and low levels in larger more advanced follicles<sup>[18]</sup> it was estimated that follicles of 5–8 mm produce approximately 60% of AMH in the serum, in a current study.<sup>[17]</sup> However, in contrast to GCs, AMH expression remains high in the cumulus cells surrounding the oocytes in larger antral follicles (10–14 mm), but only low levels of expression are found in preovulatory follicles. The pattern of AMH secretion in individual follicles has been shown to be independent of age and to remain unchanged throughout fertile life.<sup>[18]</sup>

### AMH in ovarian reserve & aging

The number of primordial follicles decreases with age and is virtually depleted at menopause. AMH serum levels determined over a three-year period in young women with normal menstrual cycles has shown a significant fall in AMH, while FSH and inhibin B remained stable. 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. The decrease of AMH levels and follicle number with age has been widely accepted.<sup>[19-21]</sup> Indeed, AMH values have greater sensitivity than inhibin B, FSH and estradiol19 values in predicting ovarian follicular reserve.

It has been reported that AMH concentrations present a negative linear correlation with basal FSH level in women who have a poor response to controlled ovarian stimulation with human gonadotropins.<sup>[22]</sup> Specifically, AMH concentrations of 1ng/ml correspond to FSH values of 10IU/L, whereas 0.5ng/ml of AMH corresponds to 15IU/L. 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.<sup>[23]</sup>

The reduction of AMH concentrations has recently been reported as a reliable marker for the evaluation of the ovarian impairment caused by chemo- or radiotherapy.<sup>[24,25]</sup> This knowledge could prove particularly helpful in fertility preservation in women subjected to such therapies.

### The role of AMH in investigating ovarian dysfunction (Hypo- and hypergonadotropic conditions)

The observed relationship between the follicular ovarian pool and serum AMH levels, indicates that serum levels could provide additional information (linked to the follicle dynamics) during the diagnostic evaluation of hypogonadism. AMH serum levels have been found to be normal in women with hypogonadotropic amenorrhea indicating that initial follicle recruitment is not abolished in hypogonadotropic hypogonadism.<sup>[26]</sup> This finding has been recently confirmed in young women with anorexia

nervosa-related amenorrhea.<sup>[27]</sup> In contrast, in women with hypergonadotropic amenorrhea (Premature Ovarian Failure, POF) serum AMH levels are very low or undetectable. In a recent study in POF patients, the number of AMH immunopositive follicles present in ovarian biopsy material was closely correlated with serum AMH levels<sup>[28]</sup>, suggesting a diagnostic role for AMH in the evaluation of hypogonadism.

#### AMH as tumor marker

Serum AMH is a good marker of tumors originating from granulosa cells. Along with inhibin its determination was successfully tested as a marker of early diagnosis and response to the treatment. AMH appeared to be more specific, while sensitivity of both

hormones was comparable.<sup>[29]</sup> The values of AMH in these patients correlated well with the size of the tumor.<sup>[30]</sup> AMH may be used also for the follow up of gonadal function in reproduction in subjects who underwent therapy possessing undesired side effects on gonads (oncological therapy, immunosuppression). In the study on females, who underwent in childhood a chemotherapy for Hodgkin lymphoma, in which lowered AMH levels reflected well a decreased ovarian reserve.<sup>[31]</sup> 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.<sup>[32]</sup>

**Table 1. Possible clinical applications of anti-Müllerian hormone levels evaluation in gynecology<sup>[31]</sup>**

1. Evaluation of ovarian follicular reserve.
  - in the general population
  - in subfertile women prior to ovulation induction
  - before and following chemo- and/or radiotherapy for cancer
2. Diagnosis and follow-up of polycystic ovary syndrome
3. Diagnosis and follow-up of ovarian tumors of granulosa cell origin
4. Prognosis of ovarian hyperstimulation syndrome risk during multiple ovulation induction

#### 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 embryologically 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.<sup>[34]</sup> 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*.<sup>[35, 36]</sup> Nevertheless further studies are required to definitively establish whether AMH has potential for clinical use in the treatment of these tumors.

#### AMH in polycystic ovary syndrome

Serum AMH is 2–4-fold higher in women with PCOS than in healthy women.<sup>[37, 38]</sup> Since AMH levels reflect the number of developing follicles, their measurement may be used as a marker of ovarian follicle impairment in polycystic ovary syndrome. PCOS is clinically diagnosed when at least two of the following three features are present: chronic oligo- or anovulation, biochemical hyperandrogenemia or hyperandrogenism and polycystic ovarian morphology in ultrasound examination (PCO).<sup>[32]</sup> The syndrome, which is diagnosed in 5-10% of women of reproductive age<sup>[33, 39, 40]</sup> is the main cause of anovulatory infertility in developed countries. The common clinical

manifestations of PCOS include menstruation disorders and androgen excess, hirsutism and male pattern alopecia.<sup>[41]</sup> polycystic ovary syndrome is also associated with metabolic aberrations. The incidence of diabetes mellitus type 2 is 10-fold higher in women with PCOS compared to healthy women in the USA.<sup>[42, 43]</sup> Furthermore, 30-50% of women with PCOS develop glucose intolerance or diabetes mellitus type 2 after the age of 30.<sup>[42-44]</sup> The incidence of metabolic syndrome is two to three-fold higher among women with PCOS compared to healthy women of similar age and body mass index (BMI), while 20% of women with PCOS, aged less than 20 years have already manifested the metabolic syndrome.<sup>[45]</sup>

#### CONCLUSION

AMH levels reflect with high accuracy the ovarian follicle reserve, and this has been demonstrated in numerous 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. Circulating AMH levels are increased in women with PCOS and its use as a clinical diagnostic marker for the syndrome has been proposed. In cases where the ultrasonographic examination of the ovaries is not feasible. AMH could be a valuable marker of ovarian reserve in the general population, which may facilitate reproductive life planning for women.

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