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Anti- Mullerian Hormone: The Guiding Light for Fertility Specialist!

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Introduction

AMH, also known as mullerian inhibiting substance (MIS), has been mainly studied for its regulatory role in male sex differentiation. AMH produced by the sertoli cells of the fetal testis, induces the regression of the mullerian ducts, the anlagen of the female reproductive tract. However, after birth, this sex dimorphic expression pattern is lost and AMH is also expressed in granulosa cells of growing follicles in the ovary.

In women, AMH expression can first be observed in granulose cells of primary follicles and expression is strongest in preantral & small antral follicles (≤ 4 mm). AMH expression disappears in follicles of increasing size and is almost lost in follicles larger than 8 mm.

Physiology:

Anti-Mullerian Hormone (AMH) is a member of the transforming growth factor β family of growth & 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 granulose cells of growing non-selected follicles makes AMH an ideal marker for the size of the ovarian follicle pool.**[**1**]**

The ovarian reserve constituted by the size of the ovarian follicle pool & the quality of the oocyte therein, declines with increasing age, resulting in the decrease of a woman's reproductive function.**[**2**]**

The size of the follicle pool is established at an early point in life. During fetal life germ cells populate the ovary & become surrounded by somatic cells forming, the so-called primordial follicles. At birth, about 1 million oocytes are present. This number decreases during childhood, resulting in a primordial follicle pool of 300000- 500000 follicles at menarche. Throughout life follicles leave the primordial follicle pool to enter the growing pool. The majority of these growing follicles will be lost as a result of atresia, unless they are rescued by FSH. This rescue by FSH starts after puberty when the pituitary gonadal endocrine axis has been activated. Among the cohort of rescued follicles, only one follicle is selected to become the dominant follicle, which will ovulate under the influence of leutinizing hormone (LH). This process continues throughout life until the primordial follicle pool is exhausted and as a consequence, growing follicles are no longer present in the ovary, resulting in menopause.

In the years proceeding menopause, fertility already decreases and the menstrual cycle becomes irregular. This menopausal transition period preceeds menopause by a fixed time interval. In the Western world, menopause is reached at a median age of 51 years. However, there is considerable

individual variation in the age of menopause and, subsequently, also in the age of subfertility. Hence, chronological age is a poor indicator of reproductive aging and thus of the ovarian reserve. **[**3**]**

To assess an individual's ovarian reserve, early follicular phase serum levels of FSH, inhibin B and estradiol (E2) have been measured. Inhibin B & E2 are produced by early antral follicles in response to FSH and contribute to the classical feedback loop of the pituitary gonadal axis to suppress FSH secretion. With the decline of the follicle pool, serum levels of inhibin B & E2 decrease & subsequently serum FSH levels rise. Because these factors are part of a feedback system, there serum levels are not independent of each other. Furthermore, changes in serum levels of FSH, inhibin B & E2 occur relatively late in the reproductive aging process. **[**4**]**

So far, assessment of the number of antral follicles by ultrasonography, the antral follicle count (AFC) best predicts the quantitative aspect of ovarian reserve. **[**5**]** However measurement of the AFC requires an additional transvaginal ultrasound examination during the early follicular phase. Therefore, a serum marker that reflects the number of follicles that have made the transition from primordial pool into the growing follicle pool, and that is not controlled by gonadotropins, would benefit both patients & clinicians. In recent years, accumulated data indicate that AMH may fulfill this role.

AMH as a marker for ovarian aging:

The quantitative aspect of ovarian aging is reflected by a decline in the size of the primordial follicle pool. Direct measurement of the primordial follicle pool is impossible. However, the number of primordial follicles is indirectly reflected by the number of growing follicles. Hence, a factor primarily secreted by growing follicles will reflect the size of the primordial follicle pool. Since AMH is expressed by the growing follicles up to selection and can be detected in serum it is a promising candidate.

In young normal ovulatory women, early follicular pool hormone measurements at 3-year intervals revealed that serum AMH levels decline significantly whereas serum levels of FSH, inhibin B and the number of antral follicles does not change during this interval. Stratification for age revealed that both serum AMH levels & number of antral follicles decline decline with age. Importantly, a strong co-relation of serum AMH levels with AFC was observed. **[**6**]**

Elevated serum levels of FSH are not found until cycles have already become irregular. Therefore, a marker that already shows a considerable change when cyclicity is still normal would better identify women with declining fertility. The usefulness of serum AMH levels as a measure of the ovarian

reserve was recently shown in young women after treatment for childhood cancer. Chemotherapy & radiotherapy treatments have adverse effects on the ovary in particular, resulting in loss of primordial follicles. Indeed, in cancer survivors, the partial loss of the ovarian reserve is reflected by increased FSH levels & decreased ovarian volume. Serum AMH levels were decreased in these patients, supporting the use of serum AMH levels as an early predictor of the ovarian reserve.**[**7**]**

AMH as a marker of ovarian responsiveness

AMH's role as a peripheral signal of the size of the growing follicle pool may have important clinical benefits. In women undergoing treatment for infertility, ovarian aging is characterized by decreased ovarian responsiveness to exogenous gonadotropin administration and poor pregnancy outcome. On the one hand, correct identification of poor responders by assessment of their ovarian reserve before entering an IVF program is important. On the other hand, assessment of the ovarian reserve may also benefit patients that would generally be excluded from IVF program because of advanced age.

Several studies have shown that AMH is an excellent marker to determine ovarian responsiveness in an IVF program. Ovarian responsiveness being defined as the number of oocytes retrieved, or as cancellation due to impaired or absent follicular growth. To achieve a reliable predictive outcome, one single hormone measurement for AMH seems sufficient. Furthermore, in contrast to FSH, inhibin B & E2, AMH levels remain relatively constant during the follicular phase & entire menstrual cycle.

AMH in ovarian reserve testing

Method	**What it assesses**
1) Follicle stimulating hormone (FSH)	Large post-antral, gonadotropin sensitive follicles
2) Estradiol	Large post-antral, gonadotropin sensitive follicles
3) Anti-Mullerian hormone (AMH)	Small post-primordial, pre-antral follicles
4) Antral follicle count (AFC)	Small post-primordial, pre-antral follicles
5) Clomid challenge test	Likely combined
6) Oocyte yield in IVF	Combined

Table 1: Methods to assess ovarian reserve

Oocyte yields are currently considered a gold standard in ovarian reserve assessment because oocyte numbers, of course, correlate well with pregnancy chances in IVF. They, however, do not represent a perfect test, since like other ovarian assessment tools, they are subject to multiple influences. After all, they only reflect end stages of folliculogenesis within the individual ovarian environments of patients. Consequently, malfunction in any one important contributing factor to this environment can negatively affect folliculogenesis and therefore, oocyte numbers as well as egg quality.

The ideal ovarian reserve test should permit identification of women who have a chance of pregnancy after IVF close to zero as a consequence of an extremely reduced ovarian reserve. The exclusion of these couples from ART could effectively reduce costs for the health system. Moreover, useless medical treatments, surgical risks, stress and disappointment could be avoided. On the other hand, the predictive value for AMH is for poor response is not absolute, with consequent false positive and negative results. Especially false positive results may have negative consequences on the couple's life since this result might incorrectly prohibit these women from undergoing IVF.

Hence, before proposing AMH measurement in the ovarian reserve testing, we should define what is the aim of the testing itself. The possible aim of ovarian reserve testing in the IVF setting is:

1) To counsel the patients about the risk/ benefit of the treatment.
2) To reduce the cost by denying treatment to bad prognosis couples.
3) To individualize treatment strategy

AMH as a marker for ovarian pathophysiology

Serum AMH level can be used as a marker for the number of growing follicles. Besides being a marker for a diminishing follicle pool, serum AMH level can also serve as a marker in ovarian pathophysiology, such as polycystic ovarian syndrome (PCOS), in which the antral follicle pool is enlarged. PCOS is one of the most common endocrine disorders in women of reproductive age. It is characterized by anovulation manifested as oligo or amenorrhea, elevated levels of circulating androgens and polycystic ovaries as visualized on ultrasound. The diagnosis is based on presence of at least two of the described characteristics, as defined by the Rotterdam Consensus 2004. PCOS encompasses a broad spectrum of clinical & biochemical characteristics. 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. The defective selection mechanism results in an accumulation of small antral follicles, which contribute significantly to the production of AMH.

In PCOS the follicular excess is mainly caused by an increase of small antral follicles upto 2-5 mm in size. Interestingly, in follicles beyond this stage, AMH expression diminishes. Therefore, it is not surprising that serum AMH levels positively correlate with the number of 2-5 mm, but not 6-9 mm, follicles in PCOS women. **[**8**]**

The ovarian aging process in PCOS women may have been slowed down, possibly due to suppressed primordial follicle outgrowth by the high levels of AMH observed in these women. However, it has also been suggested that exhaustion of the primordial follicle pool occurs later in PCOS women because their intrinsic primordial follicle pool may be increased. Data regarding the menopausal age in PCOS women are scarce. However, smaller studies seem to indicate that women with PCOS reach menopause at an older age. **[**9**]**

AMH measurement in infertile men

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.

In the 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 specrmatogenesis.**[**10**]**

Role of AMH in prediction of OHSS:

AMH is a predictor of OHSS independent of age and PCOS and is reported to be superior to age and body mass index. Its practical application is in altering the stimulation protocol in women with a high potential for developing OHSS, with the possibility of preventing it and achieving an optimal pregnancy outcome.

The role of AMH levels and over-response/OHSS has been investigated in studies which show high basal AMH levels to be a strong predictor of over-response. Some studies have also reported cut-off levels of AMH above which overresponse and OHSS may be predicted with high sensitivity and specificity.

- Predicting over-response to controlled ovarian hyperstimulation/OHSS.
- Altering stimulation protocols to prevent/minimise the chance of OHSS.
- Predicting poor response to controlled ovarian hyperstimulation.
- Altering stimulation protocols to optimise oocyte yield in predicted poor response.
- Counselling couples about poor response to avoid distress/disappointment.

Table 2: Applications of anti-mullerian hormone in fertility practice **[**11**]**

Conclusion

Serum AMH levels decrease with age in premenopausal women. Serum AMH levels correlate strongly with the number of antral follicles, suggesting that AMH levels by extension reflect the size of the primordial follicle pool. Assessment of the ovarian reserve is particularly important in IVF clinic, where AMH may be useful as a predictor of poor response. Since a considerable proportion of subfertility is due to postponement of child bearing, measurement of AMH levels to assess the ovarian reserve may also be of interest in women in general. Assessment of the ovarian reserve, at least of the size of the ovarian follicle pool, may provide insight into the number of fertile years a woman has left.

Because AMH levels are strongly correlated with the size of the follicle pool, and because of the lack of cycle variation, 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 serum AMH levels in such conditions might provide more insight into the possible cause or effect of altered AMH levels.

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