

Anti-Müllerian Hormone: A Personal View of the Empowering Analyte

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ABSTRACT

Circulating Anti Mullerian hormone (AMH) represents the total number of granulosa cells in the ovaries and is therefore a direct measure of the number of growing follicles within the ovaries. The close agreement of the main commercial assays for circulating AMH is allowing improved validation of the test in numerous circumstances. Consequently, it can be explored in all circumstances where ovarian activity may be relevant, and thereby bring improved guidance to the choices doctors and patients need to make in their reproductive lives. Apart from numerous aspects of ovarian stimulation, the main areas of impact are in endometriosis and the menopause. The best advice approach requires use of this evidence in many circumstances, and the future will see its measurement on a widespread basis.

KEYWORDS: *AMH, Ovarian reserve, Ovarian stimulation, Endometriosis, Endometriomata*

INTRODUCTION

Anti-Müllerian hormone, its origins, and its test

The recognition that anti-Müllerian hormone (AMH) can be found and measured reliably in the circulation of mature women has led to important changes in how we view many aspects of reproductive medicine in women. I make the case that it can be described as the empowering analyte because it provides critical information for women making lifetime decisions in many aspects of reproductive medicine.

AMH is a member of the transforming growth factor-beta family of glycoproteins, produced by preantral and small antral follicles, with serum concentrations reflecting both the number of these small growing follicles and the overall size of the primordial follicle pool. This new information has become a revelation in the understanding of ovarian physiology^[1] and the world of clinical reproduction and gynecology.

The sources of information for this account and overview derive from my personal role in being part of the broad teams involved in the development of the assay, and being directly involved in numerous explorations and

debates. The evidence in the section on endometriosis derives from a formal systematic review of controlled studies that provided overwhelming evidence demanding consequential debate about clinical practice.

The tests for AMH and its deployment in women

Most of the tests for AMH are based upon the assay introduced by Beckman Coulter®, using the same two monoclonal antibodies targeted to specific and different parts of the molecule as found in the circulating AMH. The assays show high degrees of reliability on all analytical platforms tested to date. Although standardisation methods vary somewhat, results obtained on one platform agree closely with those obtained on another. Tests that work to extremely low concentrations are also available, and these mostly perform well and compliantly with the main clinical assays. The AMH test is now realising its potential to provide critical information regarding choices that women may have during their reproductive life.

A circulating AMH concentration value in a mature woman is essentially a representation of the number

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Received: 09-12-2020
Accepted: 10-12-2020

Revised: 10-12-2020
Published: 28-12-2020

Access this article online

Quick Response Code:



Website:
www.jhrsonline.org

DOI:
10.4103/jhrs.JHRS_231_20

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How to cite this article: Fleming R. Anti-müllerian hormone: a personal view of the empowering analyte. *J Hum Reprod Sci* 2020;13:257-60.

of granulosa cells in developing follicles within her ovaries. Granulosa cells are found only in these follicles, and the number of them reflects the current degree of “activity” of the human ovary. By “activity,” we refer to the number of developing (growing) follicles. It is often referred to as the “ovarian reserve” although a consensus definition for this is absent. The age-related decline of follicle numbers, both nongrowing and growing, is now well defined,^[2,3] so AMH has become a marker defining the potential of the ovary on an individual basis.

Critically important in this context is the wide variability in the number of nongrowing and growing follicles between individuals of the same age. It is “normal” to see a 100 fold difference in the number of non-growing follicles in individual women^[4] and also the number being recruited into the growing cohort each month. These differences between individuals are reflected in differences in circulating AMH^[5] – and this wide range represents the intrinsic value of this measurement: the divergence between age and ovarian potential activity.

ASSERTION

The number of circumstances in which the information provided by AMH can be useful is expanding and becoming more precise through repeated validation exercises. They include focus on the menopause or premature ovarian failure, effects of cancer therapy upon reproductive potential, and of course, in the arena of fertility treatment involving ovarian stimulation. In this latter arena, it can guide how and if stimulation should be performed, and in a modern clinical situation, it would be unwise to undertake ovarian stimulation without knowledge of a woman’s ovarian reserve through AMH.

Ovarian reserve, anti-Müllerian hormone, and fertility

A woman’s fertility is broadly dictated by egg quality and quantity and both decline with age. However, in discussions around a woman’s fertility, the broad rule of thumb is that age dictates egg quality, while AMH dictates egg quantity, and options and strategies are strongly dictated by these two phenomena. Correspondingly, knowledge of a woman’s AMH allows prediction of future developments, and when combined with age, it provides critical evidence promoting logical, evidence-based advice, and decision-making. Therefore, AMH empowers individuals with evidence-based, sound decision-making.

In the developed and developing world, the increased availability and role of family planning alongside economic development has led to a profound demographic shift of delayed parenthood in increasing proportions of the world’s communities. As female fertility potential begins its inexorable decline from age 31 years,^[6] the consequences

of this phenomenon are that increasing number of women are seeking advice and clinical help regarding their fertility potential: for example, 12.5% of all women in the UK seek advice and help at some stage.^[7] At many of these considerations, knowledge of the woman’s AMH is critical to the advice given, and empowers the decision-making by the woman and her consulting doctor.

Below is a series of settings where the measurement of AMH is important and influences life choices for women.

Responses to ovarian stimulation

In standard *in vitro* fertilization (IVF), egg yields are the strongest predictor of treatment success in all age groups.^[8] AMH is the marker of choice to predict the egg yield in response to ovarian stimulation with follicle stimulating hormone (FSH).^[9] Correspondingly, women who are contemplating IVF, in its various manifestations, would be unwise to undertake such a step in the absence of knowledge of their AMH value. The reasons for this statement relate to both immediate and cumulative treatment success as well as treatment safety.

At the low extremes of AMH (concentrations <7 pm/L or 1 ng/ml), a reduced egg yield is predicted, with its consequence of reduced chances of live birth which are 50% lower than those with higher egg yields, irrespective of patient age.^[10]

At the higher extremes of AMH (concentrations above 21 pm/L [3 ng/ml] or more), the likelihood of excessive responses to stimulation increases considerably. This may have fertility benefit through an increased gamete and embryo resource, but it puts the patient at risk of the potentially fatal phenomenon of ovarian hyperstimulation syndrome (OHSS). Identifying these patients is extremely important, as there are numerous ways of addressing this issue.

One option is to attempt to attenuate the ovarian response using lower doses of FSH, which puts the patient at increased risk of suboptimal egg yields. A recent development, aiming to increase the proportion of cases with an ideal yield, involves a concept of FSH dosing dictated exclusively by patient weight and AMH concentrations. This approach can achieve a reduced incidence of OHSS and an increase in the proportion of cases with ideal egg yields.^[11] However, it does not protect against iatrogenic suboptimal egg yields^[11] as the proportion of these cases does increase. Another option of increasing popularity is to use standard doses of FSH, but trigger egg maturation with a short exposure to the luteinizing trigger for egg maturation, either with gonadotropin-releasing hormone agonist^[12] or even with Kisspeptin-54.^[13] This process obviates the development

of functional corpora lutea which are the physiological source of OHSS. The process also mandates that all embryos are cultured to blastocyst for vitrification and transferred in subsequent cycles. One recent example of this achieved a cumulative clinical pregnancy rate of approximately 70%, whilst virtually eliminating OHSS, as no embryos were transferred in the fresh cycle.^[14]

In practical terms, the guidance for ovarian stimulation can be separated into two age groups and three categories of AMH concentrations.

For women <38 years, women with high AMH values (>22 pm/L [>3 ng/ml]) IVF are valid, but there is a high risk of excessive response and OHSS. For women of this age group, with AMH between 7 and 22 pm/L (1 and 2.9 ng/ml), a healthy yield of good quality eggs can be predicted, along with an optimistic outcome. Women with AMH <7 pm/L (<1 ng/ml) can expect modest or low egg yields and therefore should be advised that success is likely to require more than one stimulated cycle.

The group of women who are 38 years or older has fewer cases in the highest category and more in the lowest, but for women of the higher two AMH categories, IVF remains a valid clinical approach, albeit with the similar risk profiles and lower pregnancy potential due to oocyte age. Older women with AMH <7 pm/L (1 ng/ml) can expect a poor fertility prognosis, and they may be best advised to consider alternative approaches.

Fertility preservation: Reproductive autonomy by choice or women undergoing treatment for cancer

Increasing number of women who are aware of the risks of delayed parenthood are attempting to mitigate them, by storing their own mature eggs through vitrification, for their own use in future. The same procedures are also being deployed in women undergoing potentially sterilizing (gonadotoxic) treatments for oncological reasons. The process is attractive to many because it preserves their chances of having their own genetic offspring, maintaining their own reproductive autonomy.^[15,16]

The method is highly dependent on sufficient egg numbers: perhaps more so than with conventional IVF. Therefore, knowledge of the patient's ovarian reserve (AMH) before undertaking stimulation is very important. Ideally, a woman who is <40 years old should be planning on preserving around twenty eggs to maximize her chances of live birth following warming and fertilization.^[17] Correspondingly, women with lower AMH may have to consider multiple courses of stimulation. This is unlikely to be recommended in women about to undergo chemotherapy.

Endometriosis

The condition of endometriosis presents a particular case where some of the issues require an improved evidence base, and development of a well-considered logical approach to management, because the consequences of surgical treatment are profound.

There is some debate as to whether the very existence of the disorder is associated with a reduced ovarian reserve (AMH). However, there is one clear and unequivocal effect of conventional management with surgical treatment when there are endometriomata present. Circulating AMH concentrations are markedly reduced over a prolonged time scale effectively a permanent impact on the ovarian reserve. Furthermore, bilateral endometriomata excision reduces the AMH more than unilateral. The degree of the treatment effect is up to 50% reduction,^[18] indicating a shortened reproductive lifespan and possibly reduced chances of success within an IVF setting. These data are important considerations for doctor/patient discussion before treatment.

The natural cycle

In general, if a woman presents with a regular menstrual cycle, then she is ovulating with an acceptable frequency, and her AMH value has little immediate importance regarding her chances of conception. However, if the concentration is low, then critical decisions regarding future fertility planning are required with some urgency. If the value is high in mature women, then there may be other considerations including a recent suggestion that there may be a link with breast cancer,^[19] although there is some way to go to determine an appropriate hypothesis.

Prediction of the menopause and premature ovarian failure

In theory, AMH should be able to predict the timing of the onset of the menopause, and it has shown potential in this regard, especially in younger women.^[20] However, the precision is not high, and correspondingly, care should be exercised. There are numerous circumstances where this may have practical value, but there is a distinct absence of enthusiasm, secondary to the weakness of the statistical link.

Polycystic ovary syndrome: Practical and theoretical features

There is surprisingly little interest in what is likely to be a critical philosophical question regarding the life-time profiles of AMH and primary oocyte recruitment in young women. In human females, the age at which the recruitment of follicles is at its maximum is in the mid-teens, around the time of puberty. In contrast, the

peak of circulating concentrations is a decade later, in the mid-20s. This phenomenon is likely to be related to increased follicular survival during that decade, leading to more granulosa cells in follicles at later stages of development.^[1] These follicles are androgenic and may be a critical component of some of the features of polycystic ovary syndrome (PCOS). Understanding the processes involved in this phenomenon would likely aid in understanding of the pathophysiology of PCOS and thereby guide therapeutic concepts. There is universal agreement that AMH provides an important guide to the diagnosis of PCOS at the clinic level, and it is therefore surprising that relatively little effort has been applied to develop it as a formal diagnostic feature, especially as normal values for female age are so well established,^[21] allowing for age-related criteria to be determined.

There is much interest and specific debate in the potential diagnostic value of AMH in PCOS, some of which is too prescriptive, but the important feature is that AMH is raised in women with PCOS reflecting their high number of developing follicles.

CONCLUSION

Before the introduction and validation of the AMH assay as a measure of ovarian reserve, the only evidential source of guidance for mature women interested in their reproductive futures, for whatever reason, was female age. With the enormous variation in ovarian reserve between individuals, well reflected in AMH measurements, that advice is irreversibly changed, adding a new dimension to the existing evidence. The future will see further validation and development of advice sources for guidance of women in the 21st century.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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