Review Article

Endocrinology Section

The Role of the **Anti-Müllerian Hormone** in **Female Fertility:** A Review

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ABSTRACT

The Anti- Müllerian hormone (AMH) is a recent biomarker for the ovarian reserve. Initially, it was considered mainly in the context of the müllerian regression and the sexual differentiation in males, but its role in ovarian functions is gaining interest very fast. It is mainly expressed in the small antral follicles and its levels decline with the growth in the follicular size. Its capability as a predictor for ovarian response can be utilised to devise a more individualised approach in the patients who opt for assisted reproductive technology (ART). It has an inhibitory effect on the primordial follicular recruitment in the ovary and on the responsiveness of the growing follicles to the follicle stimulating hormone (FSH); thus it is important in patients with polycystic ovary syndrome. This review summarizes the recent findings which concern AMH and its role in the female fertility.

Key Words: Anti- Müllerian hormone, Ovarian reserve, Ovarian response, Female fertility

INTRODUCTION

The Anti- Müllerian hormone (AMH), which is also known as Müllerian-inhibiting substance (MIS), is a member of the transforming growth factor-beta (TGF-β) superfamily, 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 [1], [2]. AMH is a homodimeric, disulfide-linked glycoprotein with a molecular weight of 140 kDa. Its gene is located on 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], [4]. AMH is strongly expressed in the Sertoli cells from testicular differentiation upto puberty and to a much lesser degree in the granulosa cells (GCs) also. It is responsible for the ipsilateral regression of the müllerian duct by eight weeks. After the involution of the müllerian system, AMH continues to be secreted, but it has no known function. Although it may have no role in the female development, its production later in life by the granulosa cells raises the possibility of autocrine and paracrine actions in oocyte maturation and follicle development [3-5].

Mechanism of Action:

The members of the TGF-β superfamily exert their effects through the serine/threonine kinase receptors. AMH acts on its own specific type II receptor, AMHR2 to signal through a BMP-like pathway, by recruiting one of the type I receptors; ALK 2, 3 or 6 [6], [7]. The downstream signalling of the AMH receptor involves cytoplasmic effectors which are known as receptor-related SMAD proteins (R-Smads 1, 5 and 8) and a common SMAD4 protein. Once AMH binds to AMHR2, the type I receptor becomes recruited, thus forming a receptor complex. This results in the activation of the type I receptor, which 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 [8], [9]. In humans, the mutations of either the AMH or the AMHR2 gene are the causes of the persistent müllerian duct syndrome [7-11].

The 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. The AMH expression in rats, mice, sheep and q 2010 human ovaries has been demonstrated by using in situ hybridisation or immunostaining. When AMH expression begins precisely during folliculogenesis is still unclear, with the studies on the primordial follicles producing equivocal results, but it is clear that the highest expression of AMH is found in the preantral and the small antral follicles, the latter being those which are involved in the follicle stimulating hormone (FSH)-dependent cyclic recruitment [12], [13]. After selection, the level of expression gradually declines in the mural GCs, with the AMH-positive staining becoming localized to the cumulus GCs. Direct measurements of the AMH protein production by the human GCs and the follicular fluid confirmed that the highest concentrations were in the small antral follicles and that they became very low or undetectable in the larger ones [14]. The cessation of production of AMH from these follicles suggests that this is an important requirement for the selection of the dominant follicle. Neither AMH staining nor AMH mRNA expression was observed in the oocytes, the corpus luteum, the atretic follicles or the theca cells in mice, rats or human ovaries, thus confirming that the GCs are the only sources of AMH in the ovary [11-15].

The function of AMH in the normal ovary:

The role of AMH in the normal ovarian function has been demonstrated with the help of AMH knockout (AMHKO) mice. These were found to be fertile, but had an increase in the number of growing follicles, thus resulting in the depletion of the primordial pool and the early cessation of ovulation, effects which were reversed by the culture of the ovaries from 2-day-old mice with AMH. These results were confirmed by the culture of mouse AMHR2-null or wild-type ovaries beneath the chorioallantoic membrane of chick embryos ('in ovo'). In this position, the pieces of tissue become vascularised, thereby preventing the normal loss of the follicles which occurs in culture [16], [17]. There was an increase in the follicle growth when compared to the wild-type, in those pieces which lacked the AMH receptor. In the human tissue, the picture was rather less straightforward. In cultured human ovarian cortical biopsies, AMH treatment (100 ng/ml) reduced the primordial follicle growth as compared to the untreated tissue, while a higher dose of AMH actually increased the numbers of the growing primordial follicles [18], [19]. In the antral follicles, the overall effect of AMH reduced the sensitivity of the follicles to FSH, as suggested by a number of in vitro studies. In rat GCs, the FSH- and cyclic adenosine monophosphate (cAMP)-stimulated aromatase activity was significantly reduced after the AMH treatment. It has also been reported that AMH reduced the aromatase mRNA expression in the cAMP stimulated cells and

reduced the luteinizing hormone (LH) receptor mRNA expression in porcine GCs which were stimulated with FSH [20]. Even in the low FSH environment of the AMHKO mouse, there was an increase in the number of growing follicles as compared to the wild-type littermates. An inhibitory effect of AMH on the FSH-stimulated aromatase mRNA expression and estradiol production has also been shown in human GCs [21], [22].

Thus, AMH performs an inhibitory role in the antral follicle growth, and it can be envisioned that high concentrations of AMH in the small antral follicles would hold back the FSH responsiveness and steroidogenesis and the acquisition of the LH receptors until the time of follicle selection. By the time the intercycle rise in the FSH occurs, the AMH production would cease, the concentrations would fall and the follicle would be 'released' to produce estradiol. However, the factors which cause the inhibition of AMH production in these selected follicles remain unknown, but the identification of this inhibitor is important, as it may provide a clue as to why the AMH production is high in polycystic ovarian syndrome (PCOS) [18], [23], [24].

There is one other important question which arises, regarding the role of AMH in these small follicles. It is well described that AMH causes the regression of the müllerian duct by inducing cellular apoptosis [25]. It is therefore interesting to speculate as to why the high concentrations in the small follicles are not similarly damaging. In the müllerian duct, atresia occurs in a pattern from cranial to caudal following the AMHR2 gradient, but why these follicles do not similarly undergo atresia due to cellular apoptosis, is not clear as yet. It may be that the ovarian cells lack the requisite intermediary pathways for this process, but no such report is still available. Therefore, the research into the role of ovarian AMH and the expression pattern of the receptor clearly needs to address this issue, taking into account the high concentrations which are found in PCOS.

Ovarian reserve and Fertility:

Ovarian reserve (OR) is a measure of the number and the quality of the eggs which are remaining in the woman's ovaries - as well as the ability of the ovaries to respond to injectable FSH stimulation. A patient's OR determines the prognostic chances of the fertility treatments and her treatment options. The best possible assessments of OR, therefore represent a core issue in modern infertility care. Various methodologies have been applied to maximize the accuracy of the OR determinations, though none have been universally accepted as superior to others. The follicle stimulating hormone (FSH) is still considered as the most widely utilized tool in routine daily practice, though the antral follicle counts and AMH have increasingly gained popularity [26], [27].

Research shows that the size of the pool of the growing follicles is heavily influenced by the size of the pool of the remaining primordial follicles (microscopic follicles in "deep sleep"). Therefore, the AMH blood levels have been thought to reflect the size of the remaining egg supply or the ovarian reserve. With the increasing ages of the females, the size of their pool of remaining microscopic follicles decreases. Likewise, their blood AMH levels and the number of ovarian antral follicles which are visible by ultrasound also decrease [27]. Women with many small follicles such as those with polycystic ovaries, have high AMH hormone values and women who have a few remaining follicles and those who are close to menopause, have low AMH levels [28], [29].

AMH levels and Conception:

Serum AMH levels in women are lower than those in men throughout life [25]. One potential advantage of using an AMH test as a marker of OR, is that it does not seem to change over the course of the menstrual cycle; FSH, on the other hand, must be measured on day 2 or day 3 of the menstrual cycle or on day 10 if it is drawn as a part of a clomid challenge test (CCT). Another point which is in favour of using it as a marker of OR is that AMH decreases with age [30], [31]. Some studies on in vitro fertilization (IVF) patients have shown lower AMH levels in women who responded poorly to fertility drugs [32-34]. A correlation was found between the number of eggs which were retrieved and the AMH levels. 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 [35-38].

The interpretation of the AMH hormone levels is also subject to variation, as the levels which are considered to be "normal", are still not clarified and agreed on by the experts. Also, different current commercial assays do not give equivalent results. Generally, the levels between 1-3 ng/ml are considered to be normal, 0.7-0.9 ng/ml to be low normal, 0.3-0.6 ng/ml to be low and less than 0.3 to be very low. The levels above 3.0 ng/ml are considered to be high and these may be associated with PCOS. But, there is a large subjective variation in the clinical interpretation [38-40].

AMH vs. other hormones as the predictors of conception:

The prediction of high ovarian response is still a great challenge in ART. There is a trend towards an individualised treatment to decrease complications, patient discomfort and cost in modern ART and it is necessary to identify the patients who are at a risk of the ovarian hyperstimulation syndrome and to use modified strategies for the stimulation, such as a gonadotropin –releasing hormone (GnRH)-antagonist regimen and mild stimulation protocols [41-43]. Numerous studies have reported that the basal serum levels of AMH or inhibin B are good predictors of the ovarian response in patients who undergo ovarian hyperstimulation and IVF [44]. Several reports also indicate that the basal serum levels of AMH are more discriminatory markers of the ovarian response than the basal follicle stimulating hormone (FSH), inhibin B, or oestradiol [45].

However, there were few reports which addressed the clinical significance of AMH and/or the inhibin B levels which were measured at the late follicular phase during the ovarian hyperstimulation. Serum and follicular AMH levels at the time of the oocyte retrieval are positively correlated with the number of mature follicles and oocytes which are retrieved [46]. A recent report indicated that the serum AMH values at the time of the human chorionic gonadotropin (hCG) administration are also correlated significantly with the number of the mature follicles, the number of oocytes which are retrieved and the serum oestradiol levels. Moreover, the AMH levels are correlated significantly with a greater number of 6-cell embryos and with better embryo morphology scores [47-49].

The serum inhibin B levels on the ovulation triggering day and the levels in the follicular fluids at the time of the oocyte retrieval are strongly correlated with the number of oocytes which are retrieved. The serum and follicular fluid levels of inhibin B at the ovum pick up are also correlated positively with the number of oocytes which are collected and are predictive of a clinical pregnancy. The serum inhibin B levels which are measured around the late follicular phase during the ovarian hyperstimulation can predict the number of oocytes which are retrieved, both in normal and poor responders [44]. Since AMH is secreted mainly in the preantral and in the early small antral follicles, the circulating AMH level decreases through the maturing follicles in the normal menstrual cycle, and further decreases in the FSH-treated cycles [16], [27]. In ovarian hyperstimulation and IVF cycles, however, the continued recruitment of the additional antral follicles during the stimulatory phase results in higher AMH levels and thus, it may be related to the number of mature follicles and the number of oocytes which are retrieved [49-51].

In contrast to AMH, inhibin B rises from the early follicular phase to reach a peak during the mid-follicular phase, but it continues to increase during the ovarian hyperstimulation. This suggests that inhibin B is secreted by the developing cohort of the antral follicles [44].

The follicular pool at the late follicular phase encompasses various

stages of follicular development during the ovarian hyperstimulation. Therefore, the AMH and the inhibin B levels at the late follicular phase could reflect the overall ovarian pool, including the small and large antral and mature follicles [38]. However, the follicular AMH levels were reported to be three times higher in the small follicles (<12 mm) than in the large follicles (>16 mm) and the serum AMH levels were tightly correlated with the follicular levels [50], [51]. These findings suggest that the serum AMH levels may reflect the small antral follicular pool more and thus we postulated that the serum AMH levels on the ovulation triggering day can be related to the number of immature oocytes which are obtained. The FSH levels, for example, may vary with the day of the menstrual cycle and may be affected by other hormone levels. A patient with an elevated oestrogen level, for instance, may have an inaccurately low FSH level. This may lead to the false assumption of normal ovarian reserves [47,52]. The only problem with the estimation of the AMH levels is the cost. Its test is quite expensive as compared to the assays of other hormones. This fact may decrease its popularity in the developing countries as a routine test [53]. But with the advent of modern biochemical techniques, there is hope for a more cost-effective method for this test.

CONCLUSION

As compared to the other ovarian tests, AMH is a much better marker for the ovarian reserve. It is more stable than FSH and does not vary from cycle to cycle. It can be measured on any day of the cycle and so, it is preferred by many fertility specialists now-a-days. It has been demonstrated to be an accurate predictor of the ovarian response in controlled ovarian hyperstimulation in ART cycles, which may result in an optimized treatment burden, in a minimization of the risk of the ovarian hyperstimulation syndrome and in increased cost-effectiveness. Increased serum AMH levels have been found in women who are affected by PCOS, thus suggesting that the serum AMH levels may also be used in the diagnosis of PCOS. The ability of AMH to inhibit the growth of the tissues which are derived from the müllerian ducts, has raised hopes about its usefulness in the treatment of a variety of medical conditions including endometriosis, adenomyosis, and uterine cancer. Research on this is underway in several laboratories.

The major problem with the measurement of the AMH levels is the cost and that only few laboratories offer this test, especially in the developing countries. But reliable test kits from trusted brands are available now-a –days and big reputed laboratories are providing this facility. If the cost of the AMH measurement is compared to that of the reproductive hormone profile (which generally includes the levels of FSH, LH and prolactin), the difference is not much. So, the affordability is comparable. The establishment of a more economical method for this test will lead to an increase in its popularity and its use in the general population. The cost will also come down with an increase in its usage. There seems to be little doubt on the fact that the research on AMH will continue in the years to come. A clearer understanding of its role in the ovarian physiology may help the clinicians to find a role for AMH measurement in the field of reproductive medicine by including it in the standard diagnostic procedures. There are other important factors that have to be taken into account while predicting the capability of a female in getting pregnant– lifestyle, infection, genetic abnormality, the quality of sperm and other male factors – but still, AMH is considered as the best hormone till date, to identify her potential reproductive capacity.

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