ANTI-MÜLLERIAN HORMONE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Anti-Müllerian hormone (AMH) is a glycoprotein produced in the granulosa cells of the ovary. It is involved in the regulation of follicular growth and development. AMH serum and follicular fluid concentration is increased in women with polycystic ovary syndrome (PCOS), which correlates with the extent of ovarian dysfunction and clinical manifestation of the syndrome. It is unclear whether the higher AMH levels in PCOS are due to the higher number of preantral follicles or result from a specific disorder in the synthesis of AMH causing follicular arrest in PCOS. AMH determination has high specificity and sensitivity as a diagnostic marker for PCOS. The AMH level can also be used to predict the effect of treatment in PCOS women, the higher values implying more difficulties in the therapeutic management of the disease.

Key words: anti-Müllerian hormone, polycystic ovary syndrome, PCOS

INTRODUCTION

Anti-Müllerian hormone (AMH), also known as Müllerian-inhibiting substance, is a member of the transforming growth factor-β superfamily, which includes more than 35 structurally related peptides, including activins, inhibins and growth differentiation factors.1-4 Most of them are involved in the reproductive function in both sexes. AMH is a 140 kDa glycoprotein four times larger than LH and FSH. The AMH gene is located on chromosome 19p13. AMH exerts its biological effect through a type II transmembrane serine/threonine kinase receptor which is expressed in the gonads and mesenchymal cells adjacent to the Müllerian ducts. Thus, AMH appears to have both autocrine and paracrine effects.1,2

Until recently, AMH was known mainly as a substance involved in male sexual differentiation. It is produced by the Sertoli cells in the testicles and induces regression of female müllerian ducts that would otherwise develop into the uterus, the Fallopian tubes and the upper part of the vagina.1-3

Although AMH can be expressed in the fetal ovarian granulosa cells of primordial follicles as early as 32 weeks’ gestation, it has important roles in postnatal ovarian function in women. It is produced by ovarian granulosa cells and is involved in the initial follicle development.5 Other effects it has in the ovaries are inhibition of the initial follicle recruitment and FSH-stimulated follicular growth, and selection of preantral and small antral follicles (Fig. 1). Serum AMH levels correlate with ovarian follicle number. Therefore, besides being able to be used as a marker of the type and extent of ovarian dysfunction, AMH may also be used as a marker of ovarian reserve and ovarian aging, because of the age-related decrease of developing follicles.1-3

AMH was first discovered in follicular fluid of women undergoing in vitro fertilization, indicating that it has an autocrine effect in follicular maturation.3,4 Antral follicles measuring less than 6 mm express the greatest amount of AMH, whereas follicles 8 mm or greater, theca cells, and atretic follicles do not express the substance. It is therefore believed that the hormone impedes the transition from primordial follicles into growing antral follicles. AMH has not yet been demonstrated to have any biologic action outside the adult human ovaries, although type II receptors have been found in adult tissues of müllerian origin.2

Serum AMH levels are almost undetectable at birth, and remain low until pre-puberty. With puberty AMH levels start to increase gradually and remain
stable throughout the reproductive life of the female. With age the levels gradually decline and AMH is undetectable in post-menopausal women.1-4

What normal levels of AMH are depend on the way they are determined in serum, but it is believed that healthy women under 38 years of age have AMH levels of 2.0 - 6.8 ng/ml (14.28 - 48.55 pmol/L).

Based on current knowledge about AMH, determination of its serum levels gives the following potential roles of the hormone as a diagnostic marker in gynecology and reproductive medicine1:
• Assessing ovarian reserve;
• Assessing the risk of ovarian hyperstimulation before ovulation induction;
• Diagnosis and surveillance of PCOS therapy;
• Surveillance of granulosa cell tumor in women;
• Ambiguous genitalia.

AMH IN POLYCYSTIC OVARY SYNDROME (PCOS)

Serum AMH levels in women with PCOS have been found to be two to three times as high as those in women with normal ovaries.6-8 This was thought initially to be due to greater number of small antral follicles. In 2007, however, it was found that the AMH production by granulosa cells in ovaries of women with PCOS was 75 times higher than that of women with normal ovaries.9 Similarly, the AMH concentration in follicular fluid of women with anovulatory PCOS is 5 times higher than that in women with normal ovaries.10 Also, the mean level of AMH in follicular fluid of women with PCOS is 60 times higher than the one in the serum.10 Other research have found that AMH levels correlate with the severity of symptoms, while in the ovulatory group concentrations are lower than those in which hyperandrogenemia is the same but they are anovulatory. It has also found that the number of follicles is only responsible for 5.3% of the increase in AMH.

These data suggest that increased production of AMH is characteristic of granulosa cells in PCOS. Evidence for this is the increased level of AMH mRNA in granulosa cells of small and large follicles in women with PCOS.11 All these studies show that increased levels of AMH in women with PCOS is primarily due to increased synthesis of AMH rather than to the increased number of follicles.

What induces the increased production of AMH in PCOS is not yet known. It may be due to many factors the most likely and obvious of which being the increased androgen production. This conclusion is made on the basis of research that has found positive correlation between androgen levels and AMH.7,8,12,13 Women with hyperandrogenism and polycystic ovaries have higher serum AMH concentrations than women with polycystic ovaries and normal androgen concentrations. A recent study by Carlsen et al. questions this hypothesis. The authors have found that 6-month depression of androgenesis with dexamethasone in women with PCOS does not lead to reduced values of AMH.14 It is possible that the concentration of androgens within the ovary is a determining factor. Another factor that could account for the elevated AMH is insulin resistance (IR) and the hyperinsulinemia typical for most women with PCOS. The studies on this are not unanimous in their findings. Positive, negative and no correlation between AMH and IR have been reported. La Marca et al. found a correlation between AMH and insulin sensitivity.15 Insulin is known to increase steroid production in granulosa cells and theca cells, hence it can be assumed that the increased concentration of AMH could be secondary - the result of the action of insulin on androgen production. Other studies have not shown such a connection and even when insulin levels decrease as a result of treatment there is no respective decrease of AMH.16 In examining 120 women without evidence of PCOS, Park et al. established a well-pronounced negative correlation between the values of insulin, blood sugar and insulin resistance and those of AMH.17 This is probably due to the direct effects of insulin on granulosa cells. It is reasonable to assume that probably the relationship of IR with AMH in women with PCOS depends on mechanisms different from those governing the growth and number of follicles. It is possible that the disparate results could be due to ethnic factors, the different anovulatory status and the degree of IR and/or hyperandrogenism.17 In the aforementioned study a positive correlation between the values of adiponectin and AMH.

Figure 1. Possible actions of AMH in the ovary. 1. Inhibition of initial follicular recruitment; 2. Inhibition of FSH-dependent growth and selection of preantral and small antral follicles.37
was established. Having in mind the influence of adiponectin and other adipokines on the action of insulin and gonadotropin hormones, it is possible that they are the likely link connecting IR with increased AMH in PCOS.

The high AMH level is thought to be associated with the pathogenesis of the polycystic ovary syndrome. An important feature of the syndrome is anovulation. Anovulation in PCOS is due to two-stage disruption of follicular development. The first is excessive follicular growth and the second - violation of the selection of one of the follicles from the increased pool and its further maturation into a dominant follicle. The hypothesis is that the high AMH levels in PCOS reduce the sensitivity of the follicles to FSH. This leads to obstruction of follicle selection and as a result - arrest at the level of small antral follicles and the inability for selection of a dominant follicle. AMH also inhibits aromatase activity, leading to a decrease in follicular production of estradiol. Low levels of estradiol also relate to the inability of selection of a dominant follicle. Another hypothesis is put forward in the latest survey of Desforges-Bullet et al. The authors establish a negative correlation between the levels of AMH and FSH in follicular fluid and the quality of ovocytes in women with PCOS undergoing IVF. Although controlled ovarian hyperstimulation facilitates the maturation of follicles in patients with PCOS, they continue to produce elevated levels of AMH, possibly due to the disruption of FSH access to follicles. Also, high levels of AMH in follicular fluid have adverse effects on the quality of ovocytes.

Elevated levels of AMH are detected in pre-pubertal and peri-pubertal daughters of women with PCOS, as well as in teenagers with PCOS, but with normal menstrual cycle. This indicates that the arrested follicular development occurs long before it can be demonstrated clinically. We can assume on the basis of these studies that early identification of risk groups for the development of the syndrome is possible. Longitudinal studies have shown that the decrease of AMH over time is less pronounced in women with PCOS than in controls, suggesting slower aging of the ovaries and later onset of menopause in these patients.

The level of AMH reflects the severity of the syndrome, since higher levels have been reported in women with PCOS and insulin resistance compared with those without IR. AMH levels are also higher in women with PCOS and amenorrhea compared with those with oligomenorrhea. The latter fact might reflect the role of AMH in the pathogenesis of anovulation in PCOS. Also, high levels of AMH may reflect significantly impaired folliculogenesis and function of granulosa cells in ovaries of amenorrheic women compared with oligomenorrheic patients. AMH levels are significantly higher in the “classical phenotypes”, meeting the criteria of the NIH from 1990 compared with the new phenotypes that emerged after the adoption of the Rotterdam criteria (hyperandrogenism + polycystic ovaries and anovulation + polycystic ovaries).

A positive correlation is established between AMH concentrations and serum testosterone, LH and the mean ovarian volume.

The determination of AMH has a high specificity and sensitivity (67% and 92%, respectively) as a diagnostic marker for PCOS. It is therefore suggested that if ultrasound criteria (number of follicles) are not sufficiently precise, they could be replaced by AMH levels as a diagnostic criterion. In a very recent study Dewailly et al. offer to overcome in this way the differences between the diagnostic criteria of Rotterdam and other criteria, and to resolve the controversy that arose after the adoption of the Rotterdam criteria regarding the various phenotypes of the syndrome. The results of this study give reasons to unite the Rotterdam and the non-Rotterdam definitions of the syndrome. To diagnose a woman as a PCOS patient after the exclusion of other diagnoses, proof of hyperandrogenism and oligo-anovulation is required. In cases in which one of these is missing, it can be replaced by the number of follicles or the estimation of AMH (Table 1). In support of this idea there are studies showing that AMH values do not change during different phases of the menstrual cycle and also after treatment with oral contraceptives. The results of a new research give reason to solve another issue related to the sometimes difficult diagnosis of PCOS in teenagers. Park et al. reveal that in oligomenorrheic girls with no evidence of hyperandrogenism AMH levels are higher than those of eumenorrheic and very close to those with proven PCOS.

In addition to diagnosis, determination of AMH may also serve as a marker for therapeutic management of PCOS. Short-term treatment with metformin (4 months) does not change AMH concentrations despite improving insulin sensitivity and ovarian morphology, while long-term (8 months) treatment reduces AMH levels. Also, the hormone can be used as a predictor of successful induction of ovulation with clomiphene citrate.
weight women with PCOS lower baseline AMH levels suggest enhanced improvement of menstrual function in weight reduction. At the same time, however, weight reduction in obese women with PCOS caused no reduction of AMH values, despite the improvement in reproductive function. It is possible in this case the changes in AMH to occur later, after a new cohort of antral follicles are recruited and begin to develop at normalized levels of androgens and insulin. In a prospective study, Amer et al. monitor the values of AMH in women with PCOS after laparoscopic ovarian diathermy. AMH decreases significantly and remains low at 3 and 6 months after the manipulation. The authors find that hormone levels before treatment can serve as a good prognostic sign with a sensitivity of 78% and specificity of 76% using a cut-off of 7.7 ng/ml.

Perhaps reduction of AMH concentration is an essential part of the reproductive response to treatment of women with PCOS and higher concentrations have a poorer prognosis. According to Pellatt et al. there seem to exist two types of women with PCOS distinguishable by the AMH level. In the first group the level of AMH is quite high and is not significantly reduced in the treatment. These women respond poorly to ovulation induction. In the second group, the levels of AMH are not so high and the treatment is more successful.

The changes in AMH levels described above may lay the basis of new therapeutic options in the future. Assuming that it is AMH that induces the arrest of follicular development characteristic of the syndrome, development of an AMH-antagonist would become the basis for a new therapeutic modality in the management of PCOS.

CONCLUSION

These data about the levels and dynamics of AMH in PCOS suggest that AMH is likely to have a role in the pathophysiology of PCOS; moreover, measuring it can provide a reliable tool for assessing the severity of the syndrome, monitoring it and predicting the effect of the treatment.

REFERENCES

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Анти-Мюллеров гормон (АМГ) представляет собой гликопротеин, образующийся в гранулезных клетках яичника и имеющий отношение к регуляции и к росту и развитию фолликулов. У женщин со синдромом поликистозных яичников (СПКЯ) концентрация гормона в сыворотке и в фолликулярной жидкости повышена, что коррелирует со степенью яичниковой дисфункции и с клиническим проявлением синдрома. Все еще остается неясным повышенное число преантральных фолликулов ли является причиной повышенных стоимостей АМГ при СПКЯ, или эти повышенные стоимости являются результатом специфического нарушения в синтезе АМГ, что со своей стороны вызывает фолликулярный арест при СПКЯ. Определение АМГ отличается высокой специфичностью и чувствительностью в качестве диагностического маркера для СПКЯ. Принимая во внимание уровень АМГ возможно также прогнозировать и эффект лечения этих женщин, при чем более высокие стоимости гормона означают меньший терапевтический эффект.