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Anti-mullerian hormone as a diagnostic marker in women with polycystic ovary syndrome

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Abstract

Plasma levels of AMH in women serves as an important biomarker of ovarian reserves and indicates the small follicular growth. The reproductive span in healthy women is predicted by progressive age related decline of plasma AMH levels. The values are low in the clinical condition of diminished ovarian reserve, indicating the presence of few remaining follicles within the ovary. Recent studies have also shown the importance of this hormone in various pathological conditions of ovary including PCOS. In women with PCOS, the small ovarian antral follicles increase and AMH secreted by these developing follicles can be used as an important marker to detect follicular impairment. It is suggested that the increased secretion of LH and/or testosterone may have a positive effect on the secretion of AMH by the ovarian follicles. A positive correlation has also been found between high AMH levels and androgen over-production due to intrinsic defects of thecal cells. In conclusion, high AMH levels have been predicted as a response to various treatments of PCOS, while improvement in various clinical and biochemical parameters have been associated with decline in AMH, thus supporting a very important role of AMH in diagnosis and treatment of PCOS.

Keywords: Anti-mullerian hormone; anovulation; Body mass Index; Polycystic ovary syndrome.

Review

Anti-Mullerian hormone (AMH) also known as Mullerian-inhibiting substance, Mullerian inhibiting factor and Mullerian-inhibiting hormone, is a glycoprotein (140kDa) encoded by *AMH* gene located on chromosome [19p13.3.] The anti-mullerian hormone interacts directly with a specific AMH type II receptor (encoded by *AMHR2* gene on chromosome 12) and thereby exhibits its function.(1)

AMH in females is produced by granulosa cells that surround the egg sac within the ovary and in fetal males by sertoli cells during embryogenesis.(2) The differentiation of sex into male and female begins with the secretion of AMH by male fetal sertoli cells and its absence in females. In male sertoli cells, the expression of AMH is activated by SOX9 and regulated by FSH, DAX1, SF1 and GATA factors.(3,4) In its absence the mullerian structures persist and develop into uterus, fallopian tubes and upper part of vagina.(5)

Plasma levels of AMH in women serves as an important biomarker of ovarian reserves and indicates the small follicular growth. The intra-follicular concentration of AMH is also dependent on the follicle size. In a normal healthy female; AMH prevents the premature development of follicles and eggs. It works by reducing the number of FSH receptors on ovaries, thus preventing the premature egg development by FSH in each cycle.(6)

The levels of AMH remain constant during the menstrual cycle as it is not secreted by primordial follicles or dominant follicle or corpus luteum.(7) However, peak values are observed in early twenties that progressively decrease until menopause.(8)

The reproductive span in healthy women is predicted by progressive age related decline of plasma AMH levels. The values are low in the clinical condition of diminished ovarian reserve, indicating the presence of few remaining follicles within the ovary. As AMH is mainly produced by the small antral follicles, it serves as a useful predictor of reproductive span of a women.(9) Recent studies have also shown the importance of this hormone in various pathological conditions of ovaries like the diagnosis and follow-up of ovarian tumors of granulosa cell origin, prognosis of ovarian hyper-stimulation syndrome and polycystic ovary syndrome (PCOS).(10)

PCOS is the most common endocrine disorder affecting women in their reproductive years and is characterized by irregular menstrual cycles, chronic anovulation and hyperandrogenism.(11) They exhibit wide range of metabolic disorders that include obesity, metabolic syndrome and the common cause for PCOS in women is hyperandrogenism.(12) About 3-10% of women with PCOS develop metabolic syndrome but the expression is highly variable between the individuals.(13-16)

The recent study showed an association of phenotypic heterogeneity with increased and variable AMH levels. According to this study, four PCOS phenotypes were identified based on the combination of anovulation (ANOV), hyperandrogenism (HA), and polycystic ovaries (PCO): phenotype 1 (ANOV + HA + PCO), phenotype 2 (ANOV + HA), phenotype 3 (HA + PCO), and phenotype 4 (ANOV + PCO). Phenotype 1 had high AMH (9.27±8.17 ng/ml) and androgen levels; phenotype 2 had low AMH (4.05±4.12 ng/ml) and were more hirsuite, phenotype 3 had intermediate AMH

levels (5.87±4.35 ng/ml) and phenotype 4 resembled controls but had higher AMH levels (7.62±3.85 ng/ml).[17]

In women with PCOS, there is an increase in the small ovarian antral follicles that are usually between 5-8mm in size and AMH secreted by these developing follicles can be used as a crucial marker to detect follicular impairment in these patients.[18] In contrast to the normal physiological condition, where primordial follicles have continuous development, PCOS women have their ovarian follicles arrested in the pre-antral and antral stages. The elevated levels of AMH has been found in all PCOS women which is related to increased number of follicles and also increased production of AMH by the individual follicular cells.[19,20] It is postulated that elevated AMH levels play an important role in the pathophysiology of anovulation associated with PCOS and an inhibitory role in folliculogenesis.[21] The clinical significance of extremely high AMH levels in PCOS women have been studied and a positive correlation of PCOS severity has been associated with elevated levels of AMH.

In vitro ovarian cell cultures from PCOS women show higher levels of AMH when compared to women with normal cycles.[22] Elevated AMH levels have been found in women with hyperandrogenemia as compared to young women with normal functional ovarian reserve {total testosterone 44.0 (32.9-58.7) vs. 23.9 (20.3-28.1) ng/dl, (P<0.05); and AMH 7.7 (6.2-9.1) vs. 2.5 (2.0-3.0) ng/mL, (P<0.05)}.[23] About 97% of women with PCOS had AMH levels > 10ng/ml that correlated positively with LH, FSH, testosterone and DHEAS levels.[24] Higher AMH levels also showed a positive correlation with testosterone, androstenedione and free androgen index.[25] The exact cause for the overproduction of AMH in PCOS women is not known, however it is suggested that the increased secretion of LH and/or testosterone may have a positive effect on the secretion of AMH by the ovarian follicles. A positive correlation was found between high AMH levels and androgen over-production due to intrinsic defects of thecal cells.[26] The AMH levels have been shown to decrease in PCOS women, when treated with metformin and oral contraceptives and it was not associated with hyperandrogenism. The mean levels correlated well with ovarian volume and both AMH and ovarian volume decreased after treatment.[27]

Recently, serum AMH levels in PCOS were shown to be a result of increased number of antral follicles and not increased synthesis of AMH per follicle. This relationship was unaffected by whether or not the women used hormonal contraception.[28] There are reports that describe higher intra-follicular levels of AMH in PCOS women compared to controls, predicting that AMH-excess could result from overactive follicles. The levels were found to be 75 fold higher in anovulatory PCOS women compared to normal women, indicating that PCOS follicles synthesize more AMH.[29]

A strong correlation was found between higher AMH level in the daughters of PCOS women and menstrual irregularities but not with clinical and biochemical features of hyperandrogenism, thus emphasizing the role of high AMH in development of PCOS among these genetically predisposed girls.[30]

Few studies have shown the impact of AMH levels on obesity in PCOS women. The levels were found to be lower in obese and overweight women with PCOS as compared to normal weight women with PCOS.[31] BMI has been associated with gene expression of AMH and AMH receptor in women with and without PCOS. A negative association was found between AMH, AMH receptor expression and BMI, in both PCOS and non-PCOS obese women.[32]

BMI appeared to significantly and correlated inversely with AMH in women with PCOS but was not associated with AMH levels in the general population of infertile women or in patients without PCOS.[33] Some studies have found no correlation between AMH and BMI. High AMH levels were suggested to be independent of adiposity and its increase was associated with androgens and not with insulin resistance.[34] HOMA-IR and insulin was significantly higher in their over-weight obese patients with PCOS but not in normal weight patients and controls. They predicted that there was not much difference in AMH between obese and normal-weight PCOS.[35] Thus AMH though a strong predictor of PCOS status cannot be related to increase BMI. In other study, serum AMH levels were found to be significantly higher in non-obese PCOS females with insulin resistance as compared to PCOS females without IR and controls.[36]

A recent study had shown that morbidly obese patients with PCOS benefitted from bariatric surgery in terms of regularization of menstrual function and normalization of serum AMH values. They found that serum AMH levels were statistically higher in patients of PCOS group pre-operatively and at the end of six months in comparison to non-PCOS patients. The AMH values reduced significantly post operatively in both groups. Non-PCOS patients had lower AMH values pre operatively and showed a trend towards reducing ovarian reserve after six months. The overall change in AMH values in both groups was statistically significant as was the normalization of menstrual irregularity.[37]

The diagnostic relation of AMH measurement along with INSL3, INH-A, INH-B has been used in laboratory finding related to hyperandrogenism. AMH and INH-A were found to be significantly higher in PCOS women compared to controls (P<0.001, P=0.008, respectively). The cut-off values for AMH and INH-A were given to be 6.1ng/mL and 12.8 pg/mL and were suggested to be used as a new biomarker in the diagnosis of PCOS.[38]

High AMH levels has been predicted as a response to various treatments of PCOS, while improvement in various clinical and biochemical parameters have been associated with decline in AMH, thus supporting a very important role of AMH in diagnosis and treatment of PCOS. Since, AMH predicts the accurate ovarian follicle reserves, its measurement may be a useful indicator of PCOS. It may be suggested as a routine diagnostic marker in these women, though large population based studies, global consensus and an international standardization of the assay are required.

Declaration of interest

The authors report no declaration of interest.

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