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Evaluation and Interpretation of AMH in Female Infertility

Kadın İnfertilitesinde AMH'nin Değerlendirilmesi ve Yorumlanması

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ABSTRACT

Anti-Müllerian hormone (AMH) is a glycoprotein that secreted by the granulosa cells of the pre-antral and antral ovarian follicles that have a diameter <8 mm. By inhibiting both initial recruitments of primordial follicles into primary follicles and also the sensitivity of antral follicles to follicle stimulating hormone (FSH) in cyclic recruitment AMH acts as a "follicular gatekeeper". AMH is recognized as an early marker of the decline in the follicular pool. Although AMH levels are accepted to be stable all through the menstrual cycle, inter- and intracycle variability are detected in the studies with the highly sensitive automated assays. Besides aging, body mass index, obesity, oral contraceptive use, previous ovarian surgery, chemotherapy, BRCA mutations, and ethnicity play a role on the AMH levels. Polycystic ovary syndrome (PCOS) is related with increased AMH level and thus proposed to be used as a diagnostic criterion. However, there is no universally accepted threshold value for AMH that can be used in the diagnosis of PCOS. AMH levels have also been used for designing an ideal treatment protocol in assisted reproduction. AMH measurements can be utilized for the prediction of poor or hyper ovarian response. The value of AMH levels in the prediction of pregnancy outcome remains controversial.
Keywords: Anti-Müllerian hormone; female; infertility.

ÖZ

Anti-Müllerien hormon (AMH), çapı 8 mm'nin altında olan pre-antral ve antral over foliküllerinin granüloza hücreleri tarafından salgılanan bir glikoproteindir. AMH, hem primordial folliküllerin primer folliküllere gelişimini hem de antral folliküllerin siklik recruitment aşamasında folikül uyarıcı hormona (follicle stimulating hormone, FSH) duyarlılığını inhibe ederek bir "folikül bekçisi" olarak görev yapar. AMH, folikül havuzundaki azalmanın erken bir belirteci olarak kabul edilmektedir. AMH düzeylerinin tüm menstrüel siklus boyunca sabit değerlerde olduğu kabul edilmekle birlikte, yüksek duyarlılıklı otomatize kitlerle yapılan çalışmalarda, hem aynı siklus içinde hem de farklı sikluslar arasında değişkenlik gösterdiği saptanmıştır. Yaşlanmanın yanı sıra, vücut kitle indeksi, obezite, oral kontraseptif kullanımı, geçirilmiş over cerrahisi, kemoterapi, BRCA mutasyonları ve etnik köken de AMH değerleri üzerinde etkiye sahiptir. Polikistik over sendromu (PKOS), artmış AMH düzeyi ile ilişkilidir ve bu nedenle tanı kriteri olarak kullanılması önerilmektedir. Bununla birlikte, AMH için PKOS tanısında kullanılacak evrensel olarak kabul edilmiş bir eşik değer belirlenmemiştir. AMH değerleri, yardımcı üreme tekniklerinde ideal bir tedavi protokolünün belirlenmesi için de kullanılmaktadır. AMH ölçümleri zayıf veya aşırı over cevabının öngörülmesi için kullanılabilir. AMH düzeylerinin gebelik sonuçlarının öngörülmesindeki yeri tartışmalıdır.
Anahtar kelimeler: Anti-Müllerian hormon; kadın; infertilite.

INTRODUCTION

Anti-Müllerian hormone (AMH) is a glycoprotein that belongs to the transforming growth factor β (TGF-β) family. In a male fetus, AMH is secreted by the immature Sertoli cells and predominantly is responsible for the regression of the fetal Müllerian ducts. In boys, AMH secretion continues until puberty and serves as a marker for differential diagnosis of sexual development disorders, hypogonadism, and cryptorchidism. In women, AMH is secreted by the granulosa cells of the pre-antral and antral ovarian follicles that have a diameter of <8 mm (1). Expression of AMH stops when the follicles reach a diameter of 8-10 mm. As AMH is expressed by the early growing follicles, its level is shown to be directly related to the primordial follicle pool (2). Moreover, researchers have demonstrated a positive correlation between the AMH levels and the antral follicle count (AFC) that represents the number of follicles with diameters of 2 mm to 9 mm (3). AMH is used as a biological marker for the evaluation of ovarian reserve as it reflects the follicular pool (4). Follicular pool assessment is designated to be used for the prediction of the number of growing follicles during ovulation induction that is related to the number of retrieved oocytes and the chance of achieving pregnancy during treatment cycles (5).

Regulation of AMH in Granulosa Cells

AMH is secreted by the granulosa cells of the growing follicle, and both AMH gene expression and AMH production is increased until the follicle reaches a diameter of 8 mm. Estradiol plays an important role in the regulation of AMH expression through estrogen receptor β (ER-β) that is present in the granulosa cells (6). Both AMH gene expression and AMH concentration are demonstrated to be negatively correlated with estradiol concentration (7) while being positively correlated with follicle stimulating hormone receptor (FSHR) and anti-Müllerian hormone receptor 2 (AMHR2) expression. Follicular fluid AMH concentration has a negative correlation with CYP19 mRNA expression, estradiol, progesterone, and inhibin-B (8). Before follicular recruitment, AMH is believed to play a role in the inhibition of aromatase (i.e., CYP19) expression while decreasing the conversion of androgens to estrogens. When the follicles reach a diameter of ≤8 mm, AMH gene and protein expression regress rapidly and a decrease in AMH gene promoter activity plays an important role in this process through ER-β. AMH has a limiting effect on follicular growth initiation in response to follicle stimulating hormone (FSH) stimulation prior to follicle selection. By inhibiting both the initial recruitment of primordial follicles into primary follicles and also the sensitivity of antral follicles to FSH in cyclic recruitment AMH acts as a "follicular gatekeeper". AMH is not shown at the cellular level after FSH-dependent follicular growth and dominant follicle selection begins. Atretic follicles and corpus luteum does not show AMH expression.

AMH has different isoforms with different molecular weights and even the same-sized follicles may contain different AMH isoforms (9).

AMH Levels during the Life-Span of Women

The AMH levels that are very low during birth in the female newborn rise gradually with increasing age until adolescence and then reach a plateau until 25 years of age (10). Serum AMH levels are negatively correlated with the age of adult women after age 25. Ethnicity is demonstrated to play a role in peak AMH levels at age 25 and the pace of age-related AMH decline in various studies (11). Due to the longitudinal decline of AMH after the mid-twenties, AMH is recognized as an early marker of the decline in the follicular pool when compared to FSH that increases only after age 35 due to the diminishing ovarian reserve (12). AMH levels become undetectable 5 years before menopause.

Is there an Intra- and Inter-Cycle Variability of AMH Levels?

Based on the preliminary studies, serum AMH levels were considered as stable all through the menstrual cycle (13), however, during the menstrual cycle variations to a degree were demonstrated in normally menstruating women and these variations were higher in younger women with higher AMH levels (14). New generation automated highly-sensitive assays have been developed for the precision of the test results as the old generation tests were manual. Besides the presence of different isoforms that can be detected differently by different assays various factors still have an impact on the measured values. Inter-cycle variability is also reported depending on the assay used and repeated measurements are performed in clinical practice in order to design an individualized treatment protocol for infertile patients.

What are the Factors Affecting Serum AMH Levels?

Body mass index (BMI), has been shown to have a negative impact on AMH levels (15), but the mechanism of this effect is not clear while leptin is believed to play a role. Some studies reported lower AMH levels in BRCA1/2 carriers and this is explained by the diminished oocyte pool related to the increased DNA damage in the oocytes in BRCA1/2 carriers although some studies showed controversial results (16). Similarly, conflicting results are published about the influence of vitamin D deficiency and vitamin D supplementation on AMH levels (16). Seasonal variations in vitamin D were reported to be parallel to the seasonal variations in AMH levels with a decreased AMH level in winter (17). Ovarian surgery especially in endometriomas and bilateral ovarian cysts is related to a decrease in AMH levels (16). Oral contraceptive use leads to a decrease in AMH levels that will recover 3-6 months after cessation of the contraceptive method (18). Chemotherapy also has a negative effect on AMH levels (16). Serum AMH levels were found to be lower in women with autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, autoimmune thyroid disease, and also women with type 1 diabetes although some of the results are inconsistent (11). In women with polycystic ovary syndrome (PCOS), the number of small antral follicles that are producing AMH is increased, and thus the serum AMH level is 2 to 3 fold increase when compared to normo-ovulatory women (19). A serum AMH cut-off value of 11.4 ng/ml was given to predict the presence of amenorrhea in women with PCOS with fairly high sensitivity and specificity by Tal et al. (20). Besides the increased number of small antral follicles, higher production of AMH from granulosa cells induced by elevated LH levels and androgen-induced FSH-independent follicular development are also reported to contribute to the higher AMH levels detected in women

with PCOS (16,21). Leptin signaling pathway and insulin resistance may also play a role in the mechanisms that lead to the elevation of AMH levels in women with PCOS. AMH levels were proposed to be integrated into the Rotterdam classification as a substitute to the ultrasonographic definition of polycystic ovarian morphology (PCOM) as one of the three criteria used for the diagnosis of PCOS. Wongwananuruk et al. (22) proposed a threshold level of 4.7 ng/ml for diagnosis of PCOS, while Song et al. (23) reported 10 ng/ml as an optimal cut-off value for differentiation between PCOS and PCOM. At present, there is no universally accepted threshold value for AMH that can be used in the diagnosis of PCOS.

Can AMH be used for the Prediction of Ovarian Response during Treatment Cycles?

Currently controlled ovarian stimulation protocols are individualized in order to obtain the optimal response that will lead to an improved pregnancy rate. Besides, individual factors such as age, BMI, AFC, basal FSH level, and serum AMH levels have also been used in the decision tree for designing an ideal treatment protocol. Serum AMH levels are currently evaluated for prediction of poor response/cancellation or hyper response and thus the risk of ovarian hyperstimulation syndrome (OHSS) and even more prediction of total fertilization failure (TFF), pregnancy, and obstetric outcome.

A cut-off level of AMH for obtaining a positive ovarian response and prediction of pregnancy in clomiphene citrate (CC) cycles was evaluated. Coşkun et al. (24) reported a cut-off value of 2.78 ng/ml for the prediction of positive ovarian response to CC in patients with unexplained infertility. Xi et al. (25) recommended the use of AMH as a predictor of ovulation induction in patients with PCOS who received CC and gave a threshold value of 7.77 ng/ml.

AMH levels were reported to be valuable in the prediction of ovarian response in in vitro fertilization (IVF) cycles as well (26). An AMH level of below 1.1 ng/ml was found to be related with TFF (27). Dose adjustment of gonadotropins used for ovarian stimulation accompanied by either gonadotropin releasing hormone (GnRH) agonists or antagonists are important in the prevention of under or overstimulated cycles. The European Society of Human Reproduction and Embryology (ESHRE) strongly recommends the use of either AFC or AMH for predicting high and poor responses to ovarian stimulation. Although serum AMH measurement is recommended over other hormonal ovarian reserve tests, a cut-off value for the prediction of low or high ovarian response is not given (28). Toner et al. (29) summarized general guidelines on the evaluation of AMH levels in patients receiving infertility treatment: AMH concentration <0.5 ng/mL may be predictive of poor outcome in IVF treatment and treatment protocols for poor ovarian reserve such as microdose GnRH agonist flare-up protocol are recommended. Patients with an AMH level of <1.0 ng/mL may have a limited chance of pregnancy during treatment cycles. Mild stimulation is recommended in patients with an AMH level >3.5 ng/mL in order to avoid the risk of OHSS (29). The cut-off values given are not age specific so it is debatable whether there is a need for the definition of age-specific low AMH concentrations.

In clinical practice, the value of AMH as a marker for ovarian reserve is widely recognized however the patients should not be excluded from IVF treatment based on the low AMH levels. Patients with very low AMH values should be counseled about the possible outcome of the treatment cycle.

There are a remarkable number of studies evaluating the association between the AMH concentrations and implantation, clinical pregnancy, and live birth rates in IVF cycles, and a negative correlation was found with lower AMH levels, however, the results remain controversial (30).

CONCLUSION

AMH is an early predictor of ovarian aging and thus is widely used for designing treatment protocols and prediction of the ovarian response in treatment cycles. However, the patients should not be refrained from IVF treatment due to low AMH levels but should be counseled about the possibility of a poor outcome.

Ethics Committee Approval: Since our study was a review, ethics committee approval was not required.

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