J Gynecol Obstet Hum Reprod 48 (2019) 19–24

Available online at ScienceDirect www.sciencedirect.com

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Review

Anti Müllerian Hormone: More than a biomarker of female reproductive function

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ARTICLE INFO

Article history:
Received 21 September 2018
Received in revised form 13 October 2018
Accepted 17 October 2018
Available online 22 October 2018

Keywords:
Anti-Müllerian hormone
AMH
Ovarian reserve
Menopause onset

ABSTRACT

Anti-Müllerian hormone (AMH), known for its role during sexual differentiation, is a dimeric glycoprotein that belongs to the transforming growth factor-β (TGF-β) family. AMH has recently been identified as a reliable marker of ovarian reserve that can help predict early ovarian follicle loss and menopause onset. AMH levels also reflect the effects of damaging gynecologic surgeries or gonadotoxic treatments such as chemotherapy on ovarian reserve. Furthermore, AMH participates in the diagnosis of certain diseases such as granulosa cell tumors or Polycystic Ovary Syndrome (PCOS). Currently used to establish patient profiles and predict ovarian response to stimulation, its role in ART techniques is crucial. Nevertheless, AMH appears to be a weak independent predictor of qualitative outcomes such as implantation, pregnancy, and live birth. As the reliability and reproducibility of AMH dosage have raised many doubts due to different existing standards and thresholds, an international consensus is still expected to improve AMH measurement and interpretation.

Introduction

Anti-Müllerian Hormone (AMH), a homodimeric glycoprotein belonging to the transforming growth factor β (TGF-β) superfamily, has first been described in the 1940s by Alfred Jost for its role in male sexual differentiation [1,2]. It is today also known for its determining role in ovarian function [3,4]. Encoded on chromosome 19, (19p13.2–13.3), its molecular weight is of 140 kDa and its signaling pathway is mediated through two serine/threonine kinase transmembrane receptors [5,6]. AMH binds to AMH type II receptor, which provokes the phosphorylation of AMH type I receptor and consequent downstream signaling through the activation of Smad proteins. After translocation to the nucleus, phosphorylated Smad proteins activate or inhibit the transcription of specific genes [7].

Biological roles of AMH

In males, the SRY gene expressed on chromosome Y is responsible of testicular differentiation. Müllerian ducts regress under the influence of AMH (produced by Sertoli cells from the end of the 7th week of gestation), and Wolffian ducts are maintained under the influence of testosterone (produced by Leydig cells). Virilization of the external genitalia is then induced by the transformation of testosterone into dihydrotestosterone (DHT).

In females, Müllerian ducts persist and develop into what will become the tubes, the uterus and the upper part of the vagina. AMH secretion by ovarian granulosa cells starts around 36 weeks of gestation, reaches a peak around 25 years of age, and continues until menopause [8]. AMH is mostly secreted by primary, secondary, pre-antral and small antral follicles (<4 mm) [9]. No AMH secretion is observed in FSH-dependent nor atretic follicles [10,11].

Most studies concerning the role of AMH in ovaries were performed in mouse model. Faster rates of primordial follicular recruitment were observed in absence of AMH, resulting in a

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https://doi.org/10.1016/j.jogoh.2018.10.015
2468-7847/

depleted ovarian reserve at a younger age [12]. In humans, an *in vitro* analysis of ovarian cortical tissue suggested that AMH was also involved in the inhibition of follicular recruitment [13]. AMH may also protect growing follicles from premature maturation by opposing the effects of FSH [14].

In an analysis of 42 women undergoing oophorectomy for benign gynecologic reasons, Hansen et al. reported a correlation between AMH levels and the number of primordial follicles present in ovarian tissue [15]. Antral follicle count (AFC – defined as the number of follicles of 2–10 mm on both ovaries estimated by ultrasound) and AMH are currently considered as the most reliable biomarkers for the assessment of ovarian reserve, which is consistent with the idea that AMH is mainly produced by small follicles [10]. Dewaily et al. suggested that Body Mass Index (BMI), menstrual cycle length, as well as FSH, LH and testosterone levels could explain discordant values of AMH and AFC observed in a same patient [16].

Measurement of AMH levels

A challenge in the interpretation of AMH dosage relies in the different standards and thresholds that exist. Serum AMH is found in different forms: an inactive non-cleaved form known as pro-AMH and a cleaved, biologically active form called AMH(N,C). AMH(N,C) is composed of N-terminal and C-terminal non-covalently associated fragments that can bind to AMH receptors (AMH RII) [17]. Pro-AMH and AMH(N,C) are detected by an immunometric method in which a capture antibody and a detecting antibody bind to the N-terminal or C-terminal portions of AMH. The existence of an isolated C-terminal form (AMHC) in serum is currently being debated.

Despite a large number of publications over the last 10 years, the reliability and reproducibility of AMH measurement have raised many doubts, mainly due to the operator-dependent manual dosing technique that uses different antibodies and thresholds: Elisa assays (mainly Beckman Gen II and EIA/AMH Immunotech) and two Anshlab assays: (Ultrasensitive (Al-105i) and Pico-AMH). Since 2014, automated dosing techniques have been developed to overcome these limitations and improve the sensitivity and reproducibility of AMH measurements. Elecsys AMH (Roche Diagnostics International) and Access AMH (Beckman Coulter) kits have shown superiority over manual assays, with 15% to 20% lower values, but have the disadvantage of using different thresholds [18]. In 2017, Peigné et al. [17] compared different AMH kits available in France: three manual (AMH Gen II, Ultrasensible Al – 105i, AL-124i or « pico-AMH) and two automated ones (Elecsys AMH, AMH Access Dxi). The two automated methods were four times more accurate, faster (18–40 min vs. 4–6 h for manual), ten times more sensitive than Elisa assays, required less serum for analysis (50 mL) and reduced 5 inter-laboratory variations [18,19]. Differences between kits were mostly observed for low AMH values. Values obtained with Acess Dxi were equal or lower to that of Gen II, and Elecsys Roche values were 12 to 28% lower. No difference was observed between the two automated assays.

A recent study reported that median values of AMH were of 2.69 ng/mL (Access) and 2.34 ng/mL (Roche) between 18 and 35 years old [20]. Anckaert et al. [21] suggested median age-specific values of AMH for normo-ovulating women with Elecsys assays: 4/3.31/2.81/2/0.882 and 0.071 ng/mL for age ranges respectively: 20–24/25–29/30–34/35–39/40–44 and 45–50 years old. International standards are expected in order to measure AMH levels accurately, as precise measurement of low AMH levels is notably important for post chemotherapy evaluation of ovarian recovery [22].

Serum AMH variations

Nomograms on AMH levels in normo-ovulatory women from birth to menopause have been developed [23,24]. The first full description of AMH production up to menopause in healthy women was lead by Kelsey et al. in 2011, showing that 34% of AMH variation was due to age. A peak of secretion of AMH is observed during neonatal life, before puberty, and around 24.5 years of age. AMH then declines until menopause. Variations of AMH levels during the first months of life can be explained by an activation of the hypothalamic-pituitary-gonadal axis during neonatal period that induces a transient increase of gonadotropins that stimulates hormone production [25]. Moreover, since AMH inhibits FSH-dependent follicle recruitment and FSH-dependent follicular growth, the production of AMH may limit inappropriate activation of follicular growth related to high rates of neonatal FSH. Between ages 8 and 24, plasma AMH concentrations remain relatively stable [26]. Small fluctuations during the pubertal transition have been reported, but appear to be minimal [27]. After a peak between 16 and 25 years old, AMH declines until menopause, reflecting the progressive depletion of ovarian reserve [23,27,28].

AMH levels do not considerably vary within and between cycles, contrarily to other hormonal markers of ovarian follicular status (FSH, estradiol, Inhibin B) [29,10]. Contradictory results were observed concerning the influence of hormonal contraception (HC) on serum AMH levels, some observing lower AMH levels in women using HC, while others did not find a significant difference [30]. Kucera et al. observed no negative impact of HC on AMH serum levels in women examined one year after termination of HC used during at least ten years [31].

Prediction of the age of menopause onset

Mean age of menopause is estimated around 51 years old [32]. Individualized counseling, early treatment or oocyte preservation can be options for patients concerned by early menopause. However, so far, no marker exists to assess the onset of menopause. AMH may be a more effective marker than FSH, menstrual irregularity, or maternal age [33,34]. AMH serum levels decline with age; starting from 21 years of age and onwards, AMH levels decrease from 5.6% per year, and become undetectable during the 3–5 years before menopause onset [35,23]. Consequently to Broer et al. [36], Depmann et al. [20] showed in a prospective study that AMH significantly predicted menopause in a model next to age. However, coherently to other studies, AMH appeared to be less effective to predict extreme menopausal ages [33,37,38].

A recent prospective study lead on 327 women concerned by early menopause showed that every AMH decrease of 0.10 ng/mL was associated to a 14% higher risk of early menopause (95% CI [1.10–1.18]; $p < 0.001$) [39]. After adjusting on demographic, behavioral, and reproductive factors, the calculated odds ratios for early menopause associated with AMH levels of 1.5, 1.0 and 0.5 ng/ml were 2.6, 7.5 and 23, respectively, compared to an AMH level of 2.0 ng/ml ($p < 0.001$). Furthermore, a meta-analysis [40] lead on 2596 patients (of which 1077 menopausal women) showed that AMH associated to age was more effective in the prediction of early menopause than age alone (Hazard Ratio: 1.01 and 95% CI [0.97–1.04] for age alone *vs.* Hazard Ratio: 0.33 and 95% CI [0.24–0.45] for age + AMH). Nevertheless, a precise AMH threshold remains to be defined and other variables such as maternal age of menopause, genetics, and lifestyle factors (smoking, BMI, use of alcohol, parity) have to be considered.

Prediction of the risk of iatrogenic amenorrhea

Treatments such as chemotherapy (CT), radiotherapy, ovarian surgery or artery embolization are known to have detrimental effects on female fertility. The ovarian toxicity of CT relies in increased apoptotic processes, cortical fibrosis and blood vessel injury and varies with age, treatment and dosage [41,42]. Alkylating agents are identified to be the most ovariotoxic existent agents, but no clear threshold yet exists for a safe alkylating agent dose [42]. Ovariotoxicity of other chemotherapy agents remains debated and poorly documented. A systemic review by Silva et al. showed that exposure to taxanes was negatively associated with menses recovery [43].

Recent studies have suggested that AMH could be used to predict ovarian follicle loss for CT patients. A study including 59 women treated with chemotherapy for early breast cancer demonstrated that long-term ovarian function after treatment could be predicted by pretreatment serum AMH concentrations and that this marker was the only significant predictor of menses after 4–5 years compared to age, Inhibin B and FSH [44]. AMH also enables to follow the evolution of ovarian reserve during chemotherapy. Anderson et al. reported a 55% decrease of AMH levels after one CT cycle and that baseline AMH levels were significantly correlated with AMH levels after the first CT cycle, as they remained higher in patients with higher baseline serum AMH levels [44]. In 2017, Dezellus et al. analyzed a large prospective multicentric cohort of 249 breast cancer patients [45]. Mean basal AMH levels were of 4.19 ng/mL (median 2.95 ng/mL). Four months after CT completion, AMH levels were of 0.78 ± 1.40 ng/mL. Women with post-chemotherapy amenorrhea were significantly older and had lower basal AMH levels than women that recovered menses [45]. Moreover, a prognostic score to estimate the time to recovery of ovarian function following chemotherapy was developed based on 109 breast cancer patients, considering age, AMH and BMI [46]. Patients with AMH levels above 0.7 ng/mL before chemotherapy, under 40 years old, and overweight or obese (BMI > 25) were more likely to regain ovarian function.

Radiation therapy is also recognized as highly ovario-toxic even at low doses, associated to extremely low or undetectable AMH dosages in post-treatment patients [47]. Furthermore, the damage of gynecological surgeries on ovarian function (endometriomas, cysts, etc.) can be evaluated by comparing pre- and post-operative AMH levels [48]. Endometrioma surgery is associated with a significant decrease in AMH levels, corresponding to an important removal of ovarian tissue [49–52], and is correlated with the bilaterality and severity of endometriomas [53]. It is therefore crucial to consider these consequences before operating patients with endometriosis that have a pregnancy desire.

AMH and fertility

It remains unclear whether low AMH levels are predictive of lower spontaneous fertility [54]. Adjusted on age, a prospective study lead on patients aged from 30 to 44 years old found lower fertility rates in patients with AMH levels under 0.7 ng/mL [55]. Conversely, by measuring biomarkers of ovarian reserve (AMH, FSH and Inhibin B) in 750 women aged from 30 to 44 years old without a history of infertility, Steiner *et al.* [56] showed that women with low AMH levels (<0.7 ng/mL) did not have a significantly different predicted probability of conceiving compared to other women, after 6 cycles (65% vs. 62%, respectively), nor after 12 cycles (84% vs. 75%). Similarly, a study of 87 women found no correlation between baseline AMH levels and time required to conceive naturally [50]. Pregnancies were reported even in women with undetectable AMH levels, particularly for young patients [57].

A study comparing three groups of patients according to AMH levels (low: <1.3 ng/mL (9.5 pmol/L), intermediate: 1.3–4.6 ng/mL (9.5–33 pmol/L), and high: >4.6 ng/mL (33 pmol/L)) observed significantly increased pregnancy rates and reduced time to pregnancy for women with high AMH levels, compared to women with intermediate and low AMH levels [58]. However, highest pregnancy rates (84.1%) were seen in regular cycling women with high AMH and spontaneous pregnancies were observed in patients with AMH levels down to 0.2 ng/mL (1.2 pmol/L) [58]. Conversely, fecundability in young healthy patients (19 to 35 years old) seems to be reduced when associated to high AMH levels (>5.5 ng/mL) (39 pmol/L) compared to AMH levels under 2 ng/mL (14 pmol/L), which could be explained by polycystic ovary syndrome patients [59].

AMH appears to be a weak independent predictor of qualitative outcomes of ART such as implantation, pregnancy, and live birth. In a meta-analysis by Iliodromiti et al. comprising 6.356 women, the predictive accuracy of AMH on live birth in women undergoing IVF was poor [60]. In a meta-analysis of 5.373 women undergoing IVF, Tal et al. [61] found that the area under ROC curve (AUC) for AMH in prediction of clinical pregnancy was of 0.63 (95% CI [0.618–0.650]).

Although an AMH threshold of 1 ng/mL (7.1 pmol/L) is usually taken, no clear AMH level threshold exists to conclude on a low, normal or increased ovarian reserve, nor on the chances of a future pregnancy [62]. As other factors most likely affect pregnancy chances, clinicians should not only rely on the dosage of AMH, but on the patient's whole clinical context. The poor predictive power of AMH for live births should thus be kept in mind when counseling infertility patients regarding ART outcomes, and low or even undetectable AMH values should not be used as a sole factor in excluding patients from undergoing ART. Moreover, clinicians should consider the psychological impact of AMH routine testing for women potentially that might lead to unjustified anxiety.

Prediction of ovarian response to stimulation: Individualized Controlled Ovarian Stimulation (iCOS)

Serum AMH values help identify patient profiles and predict response to ovarian stimulation [63]. Thus, AMH associated to antral follicular count may be the best predictive marker of hyper- or hypo-response [64]. Since 2013, dosing AMH before IVF is recommended by ESHRE (European Society of Human Reproduction and Embryology) and NICE (National Institute of Excellence for Health and Care) to individualize strategies for ovarian stimulation. The NICE consensus sets the threshold of 0.75 ng/mL (5.4 pmol/L) for a predictive low response to stimulation and that of 3.5 ng/mL (25 pmol/L) for a strong response [65]. More recently, the POSEIDON group has defined several factors, including AMH, as tools to help treatment decisions. Defined with the manual dosing technique [17], the AMH threshold associated to low response was 1.2 ng/mL (8.6 pmol/L) [66,67]. Recent data suggest that the individualization of ovarian stimulation, based on specific measurement of parameters specific to each patient, improves results while reducing treatment cost [68]. Thus, AMH is a key tool to determine the initial stimulation dose to be administered, enabling individualized counseling and strategy adjustments.

AMH: a diagnostic tool

Granulosa cell tumors

Granulosa cell tumors (GCT), the most common type of tumor of the "sex cord-stromal tumors" family, are rare tumors of variable malignancy. Although signs of clinical hyperestrogenesis or the presence of a unilateral, adnexal mass (either cystic, multilocular,

or both solid and cystic) in MRI can lead to its diagnosis, its preoperative diagnosis remains difficult to establish. Conventional ovarian tumor markers (CA125, CA19-9 and ACE) are generally elevated. By aromatizing androgens, the tumor secretes both estrogen, inhibin B, and AMH. Studies suggested AMH as a robust marker of tumor recurrence, progression and treatment efficacy in adult type GCTs, more sensitive than serum inhibin levels and more specific than estradiol levels [69–71]. Chang et al. observed a significant correlation between aggregate tumor mass and serum AMH levels, in pathological specimens and when determined non-invasively by abdominal CT or MRI [72]. Walter et al. showed that elevated AMH concentrations in female dogs were indicative of granulosa cell tumors [73]. However, negative testing does not rule out the existence of small GCTs, and differentiating granulosa cell tumors from luteinized follicular cysts may be difficult. In a meta-analysis published in 2009 evaluating the performance of Inhibin B and AMH in the diagnosis and monitoring of GCT, authors reported that the sensitivity of Inhibin varied from 89 to 100% and that of AMH from 76 to 91%, both with high specificity (91–100%) [74].

Polycystic ovary syndrome (PCOS)

Concerning 5 to 10% of women, Polycystic Ovary Syndrome (PCOS) is the most common cause of chronic anovulation and hyperandrogenism in young women. Since 2003, PCOS is defined by the Rotterdam classification (2003), requiring at least 2 out of the 3 following characteristics: (i) cycle disorder, (ii) clinical or biological hyperandrogenism, (iii) antral follicular excess on ultrasound with $\geq$12 follicles from 2 to 9 mm per ovary and/or ovarian volume $\geq$10 mL. Due to the capacity of ultrasonographic technology to detect smaller follicles, the cut off is now of 19 to 25 follicles [75,76]. This threshold is nonetheless still dependent on the operator and ultrasound equipment, and might continue to increase [77].

Since a solid correlation exists between AMH and AFC, AMH may play a role in the diagnosis of PCOS. Its use is yet not recognized in clinical practice. In vitro, AMH production by granulosa cells was found to be 4-fold higher in normo ovulatory PCOS and 75-fold higher in anovulatory PCOS compared to normal ovaries, suggesting that AMH in PCOS women is not only explained by the increase of pre-antral and small antral follicles [78]. The role of androgens has been evoked, since a positive correlation between serum androgen and number of follicles has been reported. The overproduction of androgens could be an intrinsic defect of theca cells in PCOS patient [79,80]. Serum AMH levels could therefore be correlated to the severity of PCOS symptoms (hyperandrogenism or severity of ovulation disorders).

AMH may be used as an item in the Rotterdam classification. However, no AMH threshold exists to define PCOS. With the enzyme immunoassay AMH-EIA by Beckman Coulter Immunotech, Dewailly *et al.* [76] found that serum AMH levels were a more reliable marker of polycystic ovarian morphology (PCOM) than follicle number, and suggested an AMH threshold of 5 ng/mL (35 pmol/L) to be included in the current diagnostic classifications of PCOS. In 2013, a systematic review and meta-analysis have leaned the capacity of AMH to diagnose PCOS [81]. Ten studies were included and a summary ROC curve was constructed. Using a cutoff level of 4.7 ng/mL, AMH had a 82.8% sensitivity and a 79.4% specificity for PCOS diagnosis, with an AUC of 0.87. Pigny et al. [82] recently compared threshold values according to five types of assays (tested manual assays: Gen II, EIA AMH/MIS Immunotech and Ultrasensitive Anshlab, and automatic assays: Access Dxi and Elecsys Cobas). AMH thresholds of 5.6 ng/mL (40 pmol/L) for manual tests and 4.2 ng/mL (30 pmol/L) for automated tests were defined. Despite the absence of consensus on an AMH threshold for PCOS diagnosis [82], serum AMH assays might be an interesting alternative, and are recommended by the American Association of Clinical Endocrinologists [83]. The new ESHRE guidelines published in 2018 do not recommend the use of serum AMH levels as an alternative for the detection of PCOM, nor as a single test for the diagnosis of PCOS [84]. However, it is mentioned that with improved standardization of assays and established cut off thresholds validated in large scale populations of different ages and ethnicities, AMH assays would be a reliable diagnosis tool for PCOM.

Unresponsiveness of antral follicles to FSH

Savage syndrome or unresponsiveness of antral follicles to FSH is very rare syndrome characterized by the association of primary amenorrhea, gonadotropin levels at menopausal range, and normal antral follicle count. This condition is frequently misdiagnosed and confused with ovarian failure. A normal AMH assay according to age, indicating the presence of antral follicles, could help establish its diagnosis. Although these patients are poor responders to ovarian stimulation, they may be candidates for oocyte in vitro maturation (IVM) rather than initially being oriented towards oocyte donation. The first case report on IVM in a 29-year-old Savage Syndrome patient has been published in 2013. The patient had high gonadotropin levels, normal serum AMH levels (between 4.36 and 4.50 ng/mL) and an AFC between 18 and 23 [85]. Fifteen immature oocytes were obtained, 12 of which reached metaphase II, leading to seven embryos and three transfers. A pregnancy was obtained and the patient delivered a healthy baby at term.

Perspectives

Research on AMH opens new perspectives, especially in therapeutics. Devoid of any toxicity, AMH may be a potential natural anti-cancer agent to treat tumors expressing the AMH receptor. Furthermore, the administration of recombinant AMH during treatment could reduce follicular loss induced by chemotherapy.

Conclusion

As a reliable marker of ovarian reserve, AMH plays an increasing role in the prediction of menopause onset, iatrogenic amenorrhea, and ovarian response to stimulation in ART techniques, thus facilitating individualized counseling of patients. Since no clear AMH level threshold exists to conclude on a low, normal or increased ovarian reserve, an international consensus on AMH measurement is expected.

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