Is the measurement of anti-Müllerian hormone essential?

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Purpose of review
Over the past decade, a large number of studies examining the multiple roles of anti-Müllerian hormone (AMH) have been published. The purpose of this article is to focus on the clinical usefulness of AMH in the fields of current gynecological clinical practice.

Recent findings
AMH has entered clinical practice in terms of poor ovarian response definition. It prevents folliculogenesis by reducing follicle sensitivity to follicle-stimulating hormone (FSH), and leads to anovulation when secreted in excess amounts in polycystic ovary syndrome (PCOS). Better results might be obtained in the assisted reproductive technique cycle in the presence of high AMH levels even though FSH is increased in women diagnosed with diminished ovarian reserve. In a more recently published study it has been reported that AMH can also predict the outcome of pregnancy in assisted reproduction.

Summary
AMH levels accurately reflect the ovarian follicular reserve and might, therefore, be considered as a sensitive marker of ovarian aging and ovarian reserve. Evaluation of the level of AMH has clinical value in predicting the success of in-vitro fertilization (IVF). Hyper-response/ovarian hyperstimulation syndrome (OHSS) might be anticipated as about 3.5 ng/ml or above. The cycle stability and operator independency make AMH a most appealing single marker of ovarian reserve. Use of AMH to paint tailored stimulation protocol could result in a reduced risk of OHSS, optimized treatment burden and maintained pregnancy rates. Cost-effectiveness of the use of AMH as a single test before initiating an IVF program should be determined.

Keywords
anti-Müllerian hormone, assisted reproduction techniques, obesity, ovarian reserve, PCOS

INTRODUCTION

The term ovarian reserve has been used to describe the number and/or the quality of oocytes in the ovaries [1▪]. The rate of decline in the number and/or the quality of oocytes in the ovaries may vary considerably between women of the same age. Female age remains to be the first-line marker of ovarian reserve testing in assisted reproductive techniques (ARTs) [2]. However, in view of the variation in the ovarian aging process, a test capable of providing reliable information regarding a woman's individual ovarian reserve by certain age categories would enable the clinician to provide an individually tailored treatment plan [2]. The ideal ovarian reserve test would only need one, preferably cycle-independent, measurement to represent the status of ovarian reserve [3▪▪]. The capacity of each of these tests to predict ovarian reserve is modest to poor [4] (Fig. 1). Van der Stroom *et al.* [5▪] have reported that women who bear a Down syndrome pregnancy at a younger age show signs of limited ovarian reserve, as evidenced by their frequently lower levels of anti-Müllerian hormone (AMH). Apparently measurement of AMH levels has opened new horizons in the approach to such clinical cases.

WHAT IS ANTI-MÜLLERIAN HORMONE?

Anti-Müllerian hormone is a member of the transforming growth factor super family [6▪▪]. The female

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KEY POINTS

- It is the first marker to decrease as ovarian reserve diminishes. Decrease in AMH with advancing age might be present before any changes in the currently known ageing-related variables. Serum AMH levels might be the best marker of ovarian aging and menopausal transition.
- Now, two ultra sensitive assays for AMH measurement, BC and DSL, provide similar serum AMH results.
- AMH levels appear to be related to the severity of the polycystic ovary syndrome.
- AMH concentration does not seem to be affected by the use of the oral or vaginal hormonal contraception.
- One of the three features of the Bologna criteria is about an abnormal ovarian reserve test (i.e. AFC, 5–7 follicles or AMH, 0.5–1.1 ng/ml). AMH cut-off above 1.05 ng/ml predicted better delivery chances among women with DOR, however, about 3.5 ng/ml or above which hyper-response/OHSS might be anticipated.

reproductive tract develops in the absence of AMH [7]. Serum AMH concentrations are undetectably low before puberty [8], after puberty it reaches maximum level and then serum concentrations of AMH gradually decrease as a sign of exhaustion of follicular reserve throughout reproductive life, reaching undetectable levels by menopause [9]. The granulosa cells of small antral follicles secrete AMH into both follicular fluid and the circulation [10]. Throughout reproductive life follicles consistently leave the primordial pool to develop into further stages [11]. The effect of AMH on ovarian activity seems to be complex, and the pathway of AMH activity has not been completely understood [12]. AMH is believed to participate in the regulation of release from the primordial follicle pool, hence arranging the pace at which follicles re-enter meiosis and growth, and the rate of set down of the primordial follicle pool [13]. AMH levels might reflect the continuous follicle-stimulating hormone (FSH)-independent noncyclic growth of small follicles in the ovary [14]. AMH level in the peripheral circulation is assumed to exhibit little or no fluctuation during the menstrual cycle [15] since AMH is not secreted by the dominant follicle or corpus luteum (Fig. 2). However, some authors have suggested that AMH level is indeed subjected to significant alterations throughout the menstrual cycle [16▪].

FSH*
LH
Estradiol
Inhibin B
AMH*

Transvaginal ultrasound (antral follicle count and ovarian volume)*
Doppler studies of the blood-flow in the ovaries

Clomifene citrate
Exogenous FSH
GnRH agonist

FIGURE 1. Ovarian reserve tests. Currently more commonly used ovarian reserve tests are marked with '*'.

OVARIAN RESERVE AND ANTI-MÜLLERIAN HORMONE

Serum AMH concentrations remain stable throughout the menstrual cycle, which is a major advantage over other markers of fertility such as FSH and inhibin. AMH displays less intra-individual fluctuation than the antral follicle count (AFC) both within and between cycles [3▪▪] (Fig. 3). In support of this, Rombauts *et al.* [17▪▪] have reported that follicle counts vary only minimally throughout the cycle and there is no clear advantage of performing the AFC at a particular time of the cycle. Another recent study has reported that serum levels of AMH predict the response to controlled ovarian hyperstimulation, but not quality of embryos or the outcome of pregnancy in oocyte donation [18▪▪]. Younis *et al.* [19▪] have proposed the multivariate concept to estimate the ovarian reserve. They stated that the multivariate model has the potential to predict clinical implantation and pregnancy rates in women with low and good ovarian reserve. The higher stability of serum measurements suggest that AMH might be the better cycle-independent parameter in assessing the ovarian reserve [3▪▪]. Verhagen *et al.* [4] have reported that the multivariate model is not superior to the evaluation of ovarian reserve with a single test. The cycle stability and operator independency make AMH a most appealing single marker of ovarian reserve.

METHODS FOR THE MEASUREMENT OF ANTI-MÜLLERIAN HORMONE

Two highly sensitive sandwich ELISA assays are available on the market: the Diagnostic System Laboratories (DSL) and the Immunotech-Beckman assay have both been used widely. Initial studies comparing these two assays have shown that AMH levels appear to be 4–5-fold lower [20,21] with the DSL assay compared with the Immunotech-Beckman assay. The main difference between these two assays is in the antibodies which are obtained using different standard proteins [22], thus leading

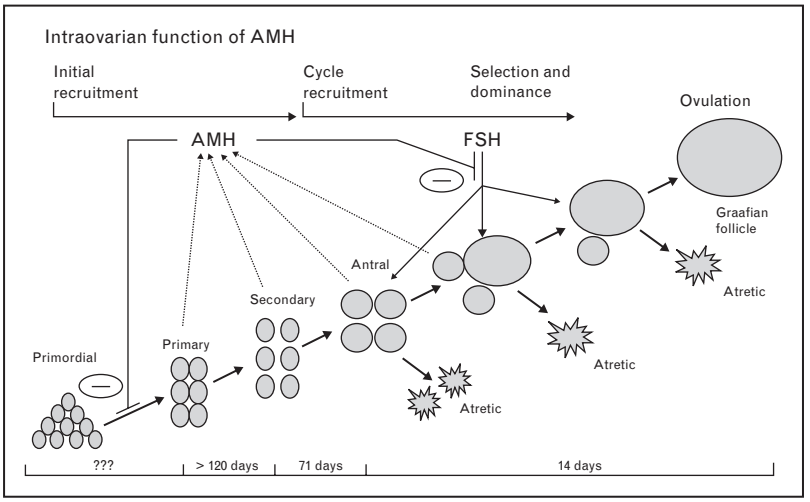

FIGURE 2. Intraovarian function of anti-Müllerian hormone (from [2]). First, AMH has an inhibitory role in the initial recruitment and thereby aids in regulating the number of follicles remaining in the primordial pool. Second, AMH has an inhibitory effect on follicular sensitivity to FSH and could therefore play a role in the process of dominant follicle selection. AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone.

to differences in assay sensitivities. Freour *et al.* [21] have compared these assays using serum obtained in assisted reproductive treatment cycles and determined clear differences in the values obtained. Although these two tests were developed independently, they are now both produced by a single company (Beckman-Coulter), and cross-referencing has shown that the correlation between the two assays is 0.9 [14]. Streuli *et al.* [23] have reported that two ultrasensitive assays for AMH measurement, Beckman Coulter and DSL, provide similar serum AMH results. Therefore the above mentioned methodological problems have been resolved by the assay manufacturer [17▪▪].

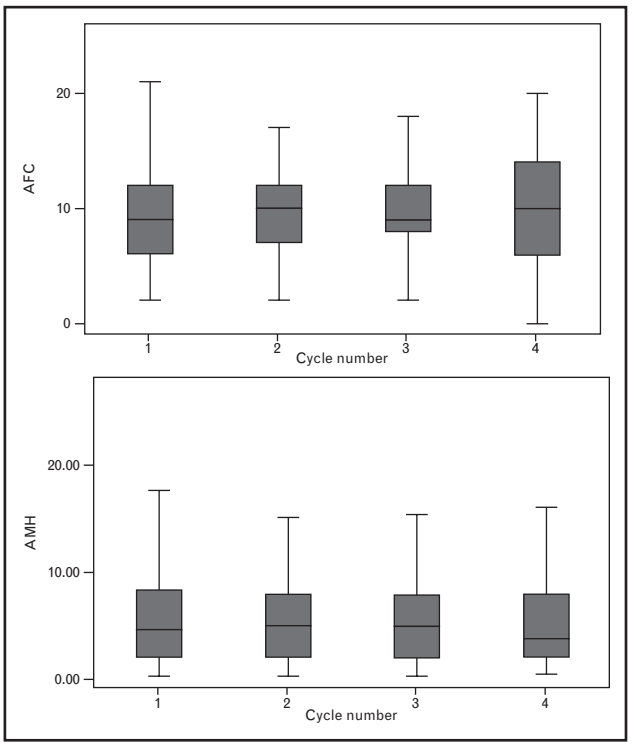

FIGURE 3. Distribution of AMH levels (ng/ml) and AFCs (of all follicles 2–10 mm in both ovaries) in the early follicular phase across four cycles. Adapted from [3▪▪].

CLINICAL USE OF ANTI-MÜLLERIAN HORMONE

Anti-müllerian hormone has entered clinical practice in several topics which will be discussed below.

Prediction of poor response and anti-Müllerian hormone

A proportion of women (2–30%) undergoing controlled ovarian stimulation (COS) experience poor response [24]. Improved counseling for the prediction of poor response may ameliorate disappointment and distress of the patient. Broer *et al.* [25] have reported that, compared to AFC, AMH has at least the same level of accuracy and clinical value for the prediction of poor response and no pregnancy. Published literatures suggest that AMH is a better marker in the prediction of poor response compared to basal FSH [2]; however, an equally good marker compared to AFC. Just recently, the Bologna criteria have been published in the European Society of Human Reproduction and Embryology (ESHRE) consensus on the definition of poor ovarian response to ovarian stimulation for in-vitro fertilization (IVF) [26▪▪]. One of the three features is about

an abnormal ovarian reserve test (i.e. AFC, 5–7 follicles or AMH, 0.5–1.1 ng/ml).

Prediction of ovarian hyperstimulation and anti-Müllerian hormone

Ovarian hyperstimulation syndrome (OHSS) is one of the most undesirable consequences of infertility treatment. It has been reported that AMH is a better predictor of an excessive response than the other patient factors including female age, body mass index (BMI), basal FSH or inhibin B [27]. It has been proposed that the dose of FSH is tailored according to the pre-IVF AMH concentration, and independently of the age and BMI of the patient [28,29]. AMH cut-off value for the prediction of hyper-response and OHSS has been calculated as about 3.5 ng/ml or above which hyper-response/OHSS might be anticipated [27,30,31▪▪]. The use of AMH to paint tailored stimulation protocol could result in a reduced risk of OHSS, optimized treatment burden and maintained pregnancy rates [3▪▪].

Polycystic ovary syndrome and anti-Müllerian hormone

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility in women of reproductive age, affecting about 7% of this population [32]. AMH levels appear to be related to the severity of the syndrome since levels have been observed to be higher in women with insulin-resistant PCOS compared to patients with normal insulin sensitivity [33]. Similarly AMH is higher in amenorrheic compared to oligomenorrheic women with PCOS [34]. AMH reduces follicle sensitivity to FSH; and therefore it might prevent folliculogenesis and lead to anovulation in PCOS [6▪▪]. AMH has also been suggested as a screening test for PCOS, which is an advantage for prepubertal girls [35▪▪]. Li *et al.* [36] have found that serum AMH measurement has a relatively poor diagnostic potency with a sensitivity of 61.7% and a specificity of 70% at 8 ng/ml in adolescent and young adult Chinese patients with PCOS.

Diminished ovarian reserve and anti-Müllerian hormone

Diminished ovarian reserve (DOR) is associated with both a decreased number and quality of oocytes retrieved during an assisted reproductive technology cycle [37], as evidenced by decreased clinical pregnancy rates. Although DOR is most often diagnosed by elevated serum FSH levels in the early phase of the menstrual cycle in clinical practice, AMH is indeed the earliest marker of DOR, with relatively minimal intra-cycle and inter-cycle variation, and its serum levels decrease well before any increase in baseline FSH [37]. Gleicher *et al.* [38] have reported that an AMH cut-off above 1.05 ng/ml predicted better delivery chances among women with DOR, although live births occurred even at undetectable AMH levels. Consequently, current literature suggests that better results might be obtained in the ART cycle in the presence of high AMH levels even though FSH is increased in women diagnosed with DOR [1▪].

Premature ovarian failure, menopause and anti-Müllerian hormone

Estimation of the age of menopause is extremely important information for women who wish to postpone their pregnancy [39▪▪,40]. Because the rate of decrease in the ovarian reserve varies fairly between individual women, development of tests that correctly predict the duration of an individual's reproductive life span would represent a major step forward [41▪▪,42]. AMH could provide an accurate assessment of the ovarian follicle pool in young hypergonadotropic patients [43]. La Marca *et al.* [14] have reported that the decrease in AMH with advancing age might be present before any changes in the currently known ageing-related variables, which indicates that serum AMH levels might be the best marker of ovarian aging and menopausal transition. Correct prediction of the age of menopause could open new opportunities in individualized prevention of age-related infertility and menopause-related conditions.

Ovarian damage and anti-Müllerian hormone

Anti-Müllerian hormone might become one of the best tests of ovarian damage due to ovarian surgery or chemotherapy. AMH measurement can be also used to predict the likelihood of response to ovulation induction drugs or laparoscopic ovarian diathermy [44]. Current findings indicate the importance of measuring preoperative and postoperative serum AMH levels as a marker of ovarian reserve to evaluate the efficacy of the surgical procedure in terms of preservation of fertility [45▪▪].

Can a single anti-Müllerian hormone measurement be used to estimate the likelihood of pregnancy prior to in-vitro fertilization?

In 2007, Nelson *et al.* [46] reported that live birth rates increased dramatically with increasing basal

AMH values independently of the age at treatment. Recently, a further large cohort study has demonstrated that serum AMH concentrations might predict live birth in women older than 34 [47]. It has recently been reported in another study that AMH can also predict the outcome of pregnancy [48▪▪].

Does anti-Müllerian hormone give us additional information in intra-uterine insemination cycles?

Li *et al.* [49▪▪] have found that serum AMH concentration was significantly higher in women with a live birth in the first cycle or cumulatively after three cycles of ovarian stimulation and intra-uterine insemination treatment, compared with those failing treatment.

Is anti-Müllerian hormone concentration affected by hormonal contraception?

Streuli *et al.* [50] have evaluated the inter-cycle and intra-cycle variations of serum AMH levels in normally ovulating volunteers and following the initiation of oral or vaginal estroprogestative contraception. Their results suggest to us that AMH concentration does not seem to be affected by the use of hormonal contraception [50] (Fig. 4). In support of the previous study, Somunkıran *et al.* [51] have reported that prolonged use (6 months) of oral contraceptives failed to induce a change in AMH levels.

Is anti-Müllerian hormone concentration affected during pregnancy and puerperium?

AMH concentration remained stable during gestation and puerperium [52]. Moreover, the fact that FSH levels were reduced throughout the gestation and during puerperium compared to the controls despite unchanged AMH levels, suggests that FSH does not play a direct role on AMH synthesis and secretion.

Is anti-Müllerian hormone concentration affected by obesity?

Obesity has been associated with reduced fertility, even in the presence of ovulatory menstrual cycles, and an increased risk of miscarriage compared with normal-weight women [53,54]. Current data suggest that AMH is negatively correlated with age and BMI [22,55▪,56]. Furthermore, weight loss intervention has been shown to result in improvement in reproductive function; however, no changes have been observed in the AMH levels in overweight and obese women with PCOS [57]. In a pilot study, authors have reported that there was a significant interaction between AMH changes with exercise and PCOS status, such that women without PCOS had no change in AMH levels, whereas women with PCOS had a decrease in AMH levels [58▪]. The results of another study also have supported that obesity has no association with levels of serum AMH [59,60▪▪]. Su *et al.* [61] have suggested that AMH levels in obese women may be lower due to physiological reasons related to obesity itself, and may not be necessarily indicative of impaired ovarian reserve. Further research is needed to clarify the effects of obesity and weight loss on AMH.

Should anti-Müllerian hormone measurement be used to deny in-vitro fertilization treatment in couples?

Although a number of markers, including AMH, may be predictive of ovarian response, none of them are 100% reliable [14]. A false-positive rate of 10–20% might be expected [22]. Therefore AMH measurement, similar to the other ovarian reserve markers, should not be used to exclude couples from IVF.

Could anti-Müllerian hormone be used as a fertility test in planning the future?

Today, most women get married at older ages or postpone having children. These women are at

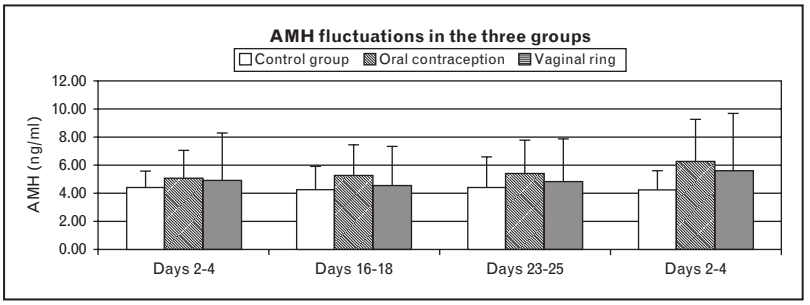

FIGURE 4. Serum AMH levels of synthetic sex steroids users and control groups throughout the menstrual cycle. Adapted from [50].

increased risk of encountering fertility issues, since ovarian reserve is significantly decreased in older women. In such cases, individuals might require information regarding their current reproductivity to plan their future families (given below).

What could random AMH level predict?

(1) Diminished ovarian reserve.
(2) Predict poor response in an ART cycle.
(3) Predict over response in an ART cycle.
(4) Individualization of treatment strategies.
(5) Number of oocytes retrieved during an ART cycle.
(6) Pregnancy outcome in an ART cycle.
(7) Assessment of ovarian reserve after reproductive surgery.
(8) Prediction of age of menopause.
(9) Predictor of how long women can safely delay pregnancy.
(10) Screening test for PCOS in adolescent.
(11) Assessment of ovarian reserve following cancer treatment.

The use of AMH may be proposed as a diagnostic test to inform patients about their chances of succeeding in assisted reproduction treatment, allowing adjustment to the already useful information derived from patient age [49▪▪]. However, it should be noted that although AMH provides information on the ovarian reserve of the individual, the use of AMH alone in planning the future might be misleading since several other factors including male infertility and tubal factor might also be present or develop in the future.

CONCLUSION

Random AMH assay might be used to individualize treatment strategies in infertility, potentially resulting in reduced clinical risks, along with optimized treatment burden and clinical pregnancy rate. The cost-efficacy of the use of AMH measurement as a single assay before entering an IVF program and whether the AMH-determined strategy of COS for assisted conception may be associated with improved live birth rate remains to be determined. Thanks to these developments, AMH will become more important in terms of women's health in the future and it will attain a more common place in clinical practice.

Acknowledgements

None.

Conflicts of interest

The authors declare no conflicts of interest.

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