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AOGS REVIEW

The use of anti-Müllerian hormone for controlled ovarian stimulation in assisted reproductive technology, fertility assessment and -counseling

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Abstract

Ovarian reserve can be determined by serum anti-Müllerian hormone (AMH) level and/or antral follicle count before controlled ovarian stimulation. The aim of controlled ovarian stimulation is to achieve an appropriate number of mature follicles and avoid complications such as ovarian hyperstimulation syndrome. Measurement of the ovarian reserve is useful for clinicians as it predicts the ovarian response to controlled ovarian stimulation. Further, it assists in giving the patient realistic expectations regarding the treatment. By determining the ovarian reserve, the most appropriate stimulation protocol and gonadotropin dose can be chosen specifically for each woman enabling so-called "individualized treatment" in line with the personalized treatment concept. Many benefits come with using AMH as a biomarker for ovarian reserve; the hormone is considered fairly cycle independent apart from a small decrease in the late follicular phase and there is no inter-observer variance. However, the use of AMH also has limitations; since the implementation of AMH in fertility treatment several AMH assays have been developed. This has made direct comparisons of AMH serum levels complicated. Currently, no international standardized assays exist. AMH is a valid predictor of the ovarian response to controlled ovarian stimulation and to some extent the chance of pregnancy in relation to assisted reproductive technology, but AMH is less optimal in prediction of spontaneous pregnancy and live birth after assisted reproductive technology. Accordingly, AMH can be used to optimize gonadotropin stimulation in fertility treatment, but is not recommended as a screening tool in the general population.

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; COS, controlled ovarian stimulation; GnRH, gonadotropin-releasing hormone; OHSS, ovarian hyperstimulation syndrome; RCT, randomized controlled trial.

Background

Treatment outcome after assisted reproductive technology (ART) varies greatly among women, so prediction of the ovarian response before fertility treatment is important for patient counseling. The ovarian response to controlled ovarian stimulation (COS) is affected by various parameters such as female age and body mass index. The antral follicle count (AFC) is used as an important predictor of ovarian response either alone or together with various other parameters. During recent years, anti-Müllerian hormone (AMH) has increasingly been used for the prediction of ovarian response to COS. The aim of this

review is to give an overview of the clinical use of AMH and to explore the available literature on the prognostic value of AMH in fertility treatment and fertility counseling.

Material and Methods

We have used the PubMed database to search relevant literature for the following predefined themes: AMH in female infertility, ovarian reserve, ovarian response, individualized stimulation protocols and in vitro fertilization (IVF). Single-case or small case reports were excluded. Papers not published in English were excluded. Overall we have mainly included systematic reviews, meta-analyses and original articles with a population of >100 women in this overview.

Ovarian reserve and ovarian response

Ovarian reserve. A newborn girl has a large pool of resting follicles (primordial follicles) in the ovaries – approximately 0.5–1 million (1). At the onset of puberty, the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus causes cyclic release of pituitary gonadotropins and cyclic recruitment of smaller antral follicles with final follicular maturation of only one large preovulatory follicle every month. AMH is produced in the granulosa cells of growing preantral and antral follicles and secreted to the follicular fluid and into the circulation (2). Hence, circulating concentrations of AMH reflect the constitution of follicles in the ovaries, predominantly those that measure 5–8 mm in diameter (3).

The true ovarian reserve is given by the number of primordial follicles left in the ovaries, and as the number of antral follicles that produce AMH correlates well with the number of primordial follicles, the hormone level can be used as a surrogate marker for the true ovarian reserve (4). However, the biomarker cannot be used as a surrogate marker for the ovarian reserve in certain situations; in women with hypothalamic amenorrhea either normal (5) or elevated AMH levels have been described (6) and in contrast, AMH is decreased in current users of oral contraceptives (7), and during long-term treatment with GnRH agonists (8). Being aware of the different hormonal values in these groups is essential to avoid false conclusions from the AMH levels.

Ovarian response. Ovarian response to COS can be defined as the number of growing follicles exceeding 10 mm or by the number of oocytes retrieved and is dependent on the ovarian reserve, the gonadotropin stimulation dose and the stimulation protocol. The stimulation protocol is chosen according to ovarian reserve markers combined with the woman's age, body mass index and ovarian response to previous IVF attempts (9). As there is variability in ovarian response to a given dose of gonadotropins, clinicians have tried to identify markers that can predict the ovarian response. The best markers to determine ovarian reserve are AFC and AMH, and both have been shown to predict the ovarian response to COS too (10).

Poor ovarian response to COS is seen in 10–20% of patients in ART treatment, with increasing prevalence among older women and reaching 50% in the group of women aged 43–44 years (11).

Women with low ovarian reserve are likely to have a poor ovarian response to COS, on the contrary women with a high ovarian reserve are at risk of an excessive ovarian response (12). Hence, the ovarian response varies greatly among women. The Bologna criteria define poor responders as women who fulfill two of the following criteria; (i) maternal age (≥40 years), (ii) previous aspiration of three or fewer oocytes after COS, or (iii) an abnormal ovarian reserve test being either an AFC of five to seven follicles, or low AMH level of 0.5–1.1 ng/mL (3.6–7.9 pmol/L) (11). A more recent paper did not find AMH cut-off values that were universally adopted. According to this update, a cut-off value of AMH between 0.7 and 1.3 ng/mL may be acceptable for the prediction of poor response before IVF (9).

In a systematic review, a low AMH cut-off level of 0.1–1.66 ng/mL (0.71–11.86 pmol/L) is found to have sensitivities ranging between 44 and 97% and specificities ranging between 41 and 100% for prediction of poor ovarian response (13). Broer et al. performed an individual patient data meta-analysis in 2013 (n = 5705) comparing the predictive value of AMH and AFC for poor response after IVF (10). The group found that similar accuracy is reached with either of the two tests, and combining the two tests does not improve the predictive value. A different paper also finds similar predictive value for ovarian response when comparing AFC and AMH (n = 1259) (14).

However, AMH shows a stronger correlation with oocyte yield compared with AFC (n = 749) and is a better predictor of poor and high ovarian response in good-

Key Message

Anti-Müllerian hormone predicts the ovarian reserve and is used in assisted reproductive technologies to titrate the gonadotropin stimulation treatment with the lowest risk of complications. The biomarker predicts oocyte yield rather than chances of achieving pregnancy and live birth.

prognosis patients undergoing a short GnRH antagonist treatment (15). A multi-center study (n = 1205) confirms this finding as it examined the ability of AMH to predict ovarian response in good-prognosis patients using GnRH agonist or GnRH antagonist protocols (16). The conclusion is that AMH is a better predictor of oocyte yield than AFC. However, in this study, expected poor-responders were excluded.

Ultimately, both AFC and AMH levels can predict whether a woman is likely to respond to exogenous gonadotropins with a poor, normal or hyper-response (17); with increasing serum AMH levels an increased response to COS follows (15). Recent findings have suggested that dynamic AMH levels during COS correlate with ovarian response as it reflects the follicular development during COS (18). This represents a new opportunity in the usage of AMH as the decline in the hormone value during COS is associated with oocyte yield.

Individualization of COS

Ovarian hyperstimulation syndrome. As described above, clinicians decide on the optimal stimulation treatment strategy before IVF based on the expected ovarian response (12). The aim of COS is to aspirate 7–14 oocytes as seven or more are considered to give a fair chance of achieving pregnancy (19) and it has been shown that the risk of developing severe ovarian hyperstimulation syndrome (OHSS) increases when there are more than 15 mature follicles on the day of triggering final oocyte maturation (20).

A potentially life-threatening condition, OHSS is an exaggerated response to COS (21). The complication has onset in the luteal phase and/or early pregnancy after ART causing cystic enlargement of the ovaries and a rapid fluid shift from the intravascular compartment to the transcellular space causing ascites, hypercoagulability and electrolyte imbalances. Serious complications such as pleural effusion and acute renal insufficiency have been reported in women with severe OHSS. Moreover, women developing OHSS have increased levels of hemostatic markers following the fluid shift and are therefore at a higher risk of developing venous thromboembolism. A paper concludes that the risk of venous thromboembolism related to OHSS in the first trimester is 1.7%, which is a 100-fold increase compared with the background non-IVF population (22). Hence, the risk of developing OHSS has to be considered for women undergoing COS (23), balanced by the risk of cycle cancellation due to low ovarian response. Women with low AMH levels are at risk of poor ovarian response and therefore higher doses of gonadotropins are typically applied trying to maximize follicular recruitment and oocyte yield. In contrarst, in women with high AMH levels, a milder stimulation protocol with lower doses of gonadotropins are often used to reduce the OHSS risk (17).

In 2013, Broer et al. carried out an individual patient data meta-analysis (n = 1023) exploring the predictive value of biomarkers according to excessive response to COS (24). They found similar predictive capacities of AMH and AFC and showed that the best prediction is made when combining the two markers makes the receiver operator curve analysis of the area under the curve 0.85. Adding female age to the model does not improve the area under curve. Cut-off AMH levels of 1.59–7.00 ng/mL (11.36–50.00 pmol/L) have been found to have sensitivities ranging between 40 and 95% and specificities ranging between 31 and 96% in predicting excessive response to COS (25).

Even though there is no universal serum AMH threshold that eliminates the risk of OHSS (25), AMH levels are widely used to adjust the starting dose of gonadotropins. There is increasing evidence that individualized COS can reduce OHSS and/or preventive interventions (9,26,27), and this reduction might lead to reduced costs and possibly fewer couples dropping out of ART programs.

Ongoing pregnancy rates and live birth rates are equal among women treated in a short GnRH antagonist protocol and in a long GnRH agonist protocol (n = 1050) but the risk of developing OHSS is significantly higher when treated in the long protocol (28). Hence, the use of a short GnRH antagonist protocol should be the treatment of choice in women with high basal AMH who are predicted to have a high ovarian response. In the case of an excessive ovarian response and a high risk of OHSS, a GnRH agonist trigger can be used with or without a freeze-all strategy (29). A short protocol with GnRH agonist trigger and a freeze-all strategy can almost eliminate the development of OHSS. Vitrification of all oocytes in women at risk of developing OHSS (n = 96) reduces the risk of OHSS and results in significantly higher pregnancy rates when compared to women who have been treated with the classical coasting treatment which involves withdrawing gonadotrophin treatment until the serum estradiol level fall to an acceptable level (n = 152) (30). In a Chinese randomized controlled trial (RCT), the freeze-all strategy results in higher live birth rates in 1500 PCOS patients (31). Yet, the freeze-all strategy is not implemented as standard care at fertility clinics owing to a lack of RCTs in patient categories other than women with a high ovarian response. Currently a multicenter RCT is underway in Denmark and Sweden comparing the freeze-all strategy with a fresh-transfer strategy in women with an expected normal ovarian response without PCOS (32).

Dosage algorithms. Different dosage algorithms are used to titrate the gonadotropin dose specifically for each

woman, making individualized treatment possible. The algorithms incorporate varying numbers of predictors such as age, body weight and ovarian reserve tests. Table 1 shows an overview of studies testing different dosage algorithms.

In 2009 a prospective cohort study (n = 538) including women undergoing IVF treatment suggested that AMH can be used as a determinant to individualize stimulation strategies for COS (33). Based on their serum AMH levels, women are predefined as likely to have a poor, normal or high ovarian response to stimulation treatment. The groups are treated with diverse stimulation protocols irrespective of age; the long GnRH-agonist protocol is administered to women predicted to have a normal ovarian response and the short antagonist protocol is administered for the predicted poor and high responders. Also, the gonadotropin starting dose decreases with increasing AMH levels. The study concludes that individualized treatment reduces the risk of hyper-response while maintaining equal pregnancy rates.

A recent RCT allocated women (n = 308) undergoing IVF treatment to one of two dosage algorithms; one including age, body mass index, AFC and AMH and one including age, body mass index and AFC (34). Adding AMH to the dosage algorithm did not increase the number of women who had a normal ovarian response – in fact, a significantly higher proportion of women had a low ovarian response in the group where AMH is added to the algorithm. There is no difference in the total gonadotropin dose between the two groups and no significant

Table 1. Features of the studies testing different dosage algorithms for controlled ovarian stimulation.

Author	Year	Design	Participants	Pro-/ retrospective	Intervention	Primary outcome	Conclusion
Nelson et al. (33)	2009	Cohort study	538	Prospective	Adjustment of FSH daily dose based on AMH levels at the beginning of COS	OHSS and clinical pregnancy rates	A single measurement of AMH can be used to individualize treatment strategies and result in lower incidence of OHSS
Anckaert et al. (35)	2012	Cohort study	731	Retrospective	A fixed starting dose of HP-hMG or rFSH. Gonadotropin dose-adjustment on stimulation day 6 was decided based on AFC	Oocyte yield	AMH level at the beginning of COS was significantly associated with the number of oocytes retrieved and predicts the need to adjust the gonadotropin-dose on stimulation day 6
Allegra et al. (27)	2017	RCT	191	Prospective	FSH starting dose based on either a dosage algorithm (age, day 3 FSH and AMH) or on age	No. of patients with an optimal oocyte yield (8–14)	Optimal response 58/92 (63%) in the algorithm group, 42/99 (42%) in the control group. FSH starting dose based on ovarian reserve is associated with a higher proportion of patients with an optimal response
Andersen et al. (26)	2017	RCT	1329	Prospective	rFSH dosage based on s-AMH and body weight or dosage with conventional follitropin-α	Ongoing pregnancy and ongoing implantation rate	Ongoing pregnancy 30.7% vs. 31.6%, no significant difference. Implantation rate 35.2% vs. 35.8% no significant difference. Using individualized dosage of rFSH results in same efficacy and improved safety
Magnusson et al. (34)	2017	RCT	308	Prospective	COS based on a dosage algorithm including AMH, age, AFC and BMI	No. of women with an oocyte yield between 5 and 12	Dosage regimen including AMH compared with non-AMH dosage did not improve the oocyte yield

AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; COS, controlled ovarian stimulation; FSH, follicle-stimulating hormone; HP-hMG, highly purified human menopausal gonadotropin; OHSS, ovarian hyperstimulation syndrome; rFSH; recombinant FSH; s-AMH, serum AMH.

difference in the rates of OHSS. As the study compares two different dosage algorithms, results provide no answer to whether a dosage algorithm using AFC/AMH is superior to a standard algorithm. The study did not compare the interchangeability of AMH and AFC, but using AMH results in no added value to the model (10).

Anckaert et al. demonstrate (n = 731) that gonadotropin dose-adjustment on stimulation day 6 based on the follicular development can be estimated based on the AMH level (35).

Individualized algorithms for gonadotropin stimulation have not yet proven to increase pregnancy and live birth rates, however they lower the risk of OHSS, hence increasing patient safety.

AMH and the chance of achieving pregnancy

Achieving pregnancy after COS. While AMH is a predictor of oocyte yield after COS, the literature shows no evidence of AMH being a valid predictor of the chance of achieving pregnancy after COS. Female age is the most accurate predictor for ongoing pregnancy after IVF (10).

A meta-analysis including 5764 women with unknown ovarian reserve undergoing IVF explores the association between AMH and live births (36). They conclude that the ability to predict live birth based on AMH is poor as they find a sensitivity of 83.7% (95% CI 72.5–90.9%) and a specificity of 32.0% (95% CI 21.6–44.6%). In a study based on 749 good-prognosis patients using both fresh and cryopreserved oocytes, an association between AMH level and cumulative pregnancy rate and live birth rate is found; however, the authors conclude that the association is due to a higher oocyte yield and not a better oocyte quality (15).

In a recent meta-analysis including more than 5300 women undergoing ART AMH is associated with implantation and pregnancy rates, but generally AMH is found to be a weak predictor of these outcomes (37).

High AMH levels are associated with a higher oocyte yield after COS, but not necessarily with a better oocyte quality. Low levels of AMH are associated with poor ovarian response and a lower pregnancy rate, but the hormone level is not an absolute indicator of the outcome after COS (38). In 2013 Mutlu et al. performed a study on women undergoing IVF treatment (n = 192) and concluded that only age could predict the chance of live birth (39). With low AMH levels there are still reasonable pregnancy and live birth rates, especially for younger women (40,41).

AMH as a predictor of natural fertility. The use of AMH as a predictor of natural fertility has been studied in a number of papers. A Danish cohort study (n = 186) from 2012 including healthy, regularly cycling women in their mid-20s who were trying to conceive concludes that AMH cannot be used to predict the chance of conceiving as the time to pregnancy is not prolonged with lower AMH levels (42). This is confirmed in a recent paper (n = 279), which finds that high fecundability is associated with low AMH values (43). Somewhat unexpectedly, time to pregnancy is shortest in the quintile of women with the lowest AMH levels, but a part of the reason for this is probably that anovulatory women are included in the study. A recent Danish study including women referred to ART (n = 382) aged 20–39 years concludes that infertile women do not have diminished AMH level compared with controls with no history of infertility when adjusting for age (44). However, this study includes anovulatory women too and consequently the infertile group in this study expectedly has higher AMH values. In an American study (n = 100) including slightly older women aged 30–44 years, low AMH levels are associated with reduced fecundability (45). As the literature is not conclusive, large prospective studies are needed to establish the association between AMH levels and natural fecundability.

Challenges and benefits of using AMH

Fluctuations in AMH. Increasingly, AMH is being chosen as the preferred biomarker in fertility assessment. When using AFC the antral follicles are counted but so are the atretic follicles even though they will respond poorly to COS (46). This miscalculation is avoided when using AMH; however, some inter-cycle variability in AMH has been reported.

The serum AMH level is generally considered rather cycle-independent allowing measurement at any given time during the menstrual cycle. However, studies have shown some intracyclic variation (47), and a recent systematic review (n = 2163) demonstrates that fluctuations in serum AMH reflect the fluctuations in AFC (48), and the hormone level decreases towards the end of the follicular phase when the dominant follicle is recruited (49).

Overbeek et al. look at 44 healthy, regularly menstruating women and find that a low AMH value results in low fluctuations in the hormone level during the menstrual cycle and therefore a single measurement of AMH in this group of women can be justified. In women with a normal to high hormone level the fluctuations are higher and therefore it might be necessary to have more than one measurement in this group (50).

Somehow contradictory, a larger study including more than 3000 women shows that one-third of the intracyclic variation is due to aging (51) and it has been shown that

the variation is more pronounced in older women (49,52).

In a recent published ESHRE abstract (2017) 27 healthy women are followed for three menstrual cycles and blood samples are taken on different cycle days showing a significant variability in AMH levels throughout the menstrual cycle (53).

A circadian variation in the AMH level has also been demonstrated. A study (n = 20 women) compares blood samples taken every second hour during 24 h and finds a mean difference in AMH level of 1.9 pmol/L (54), the lowest level being at 4.00 a.m. (mean 16.0 pmol/L) and the highest being at 4.00 p.m. (mean 18.1 pmol/L). This explains that a repeated measurement of AMH can result in variability (55).

Some small fluctuations in AMH during the menstrual cycle are to be expected, probably due to the biological variation in the number of viable smaller AMH-producing follicles when one follicle reaches dominance. Even so, AMH is still the most stable endocrine marker for the ovarian reserve (56). The fluctuations are probably of minimal clinical relevance, but there is still room for further investigation.

Assays for measuring AMH. As AMH was introduced as a biomarker in fertility treatment several new assays have been developed causing difficulties in the comparison of AMH levels measured with different assays (55). Previously the most used assay was a sensitive second-generation assay, the AMH Gen II ELISA (marketed by Beckman-Coulter, Brea, CA). However, some studies challenged the reliability of the Gen II assay as within-subject variability and complement interference were well-documented (57). Beckman-Coulter modified the assay to include a predilution step to avoid interference from complement binding, and new AMH measurement kits have been developed including the Ultra-Sensitive AMH/MIS ELISA kit (Ansh Labs, Webster, TX), the automated Access AMH assay (Beckman-Coulter Diagnostics) and the Elecsys AMH Immunoassay (Roche Diagnostics International Ltd, Basel, Switzerland). Comparison of these assays show a good correlation between the new assays and the Gen II assay, but the results obtained from the Elecsys assay are lower (0.88-fold) than the AMH values measured with the Gen II assay (58). Also, an assay directed at measuring very low values of AMH has been developed, the picoAMH assay (Ansh Labs). AMH levels measured by the picoAMH assay are correlated to the Gen II assay (59), but measurements with picoAMH are 69% higher than the Gen II assay. Further, 78% of the values being undetectable with the Gen II assay can be measured with the picoAMH assay. Conclusively, very low levels of AMH < 3 pmol/L can be detected with the picoAMH assay and the Elecsys AMH Immunoassay (59,60) making it possible to explore the association of AMH and treatment outcome in women with very low ovarian reserve, yet the absolute numerical values do differ between different assay platforms. This difference in absolute numerical values between assays needs to be emphasized as it is not possible to draw consensus cut-offs for clinical applications until an international standard is available, making an international standard urgently needed.

Conclusion

Before fertility treatment the ovarian reserve can be determined via AFC and AMH as these tests predict the ovarian response to COS. This helps clinicians to choose the optimal treatment strategy and to provide women with realistic expectations before treatment; however, AMH is a less good predictor of the chance of live birth. Different AMH assays have been developed, however, no international assay standard for measuring AMH exists, which is highly needed. AMH as a single measurement should not be used as a screening tool for natural fecundability in the general population, but longitudinal studies with repeated AMH values for the same women over time may be used to determine the velocity of the AMH decline and hence the depletion of the primordial follicular pool.

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