Review Article

Anti-Mullerian Hormone and Fertility Treatment Decisions in Polycystic Ovary Syndrome: A Literature Review

Duru Shah, Padma Rekha Jirge[1]

Gynaecworld, The Centre for Women's Health and Fertility, Mumbai, [1]Sushrut Assisted Conception Clinic, Shreyas Hospital, Kolhapur, Maharashtra, India

Abstract

Anti-Mullerian hormone is a robust marker of ovarian reserve and ovarian response in *in vitro* fertilisation (IVF). However, its role extends beyond improving the safety of IVF by aiding in choosing appropriate protocols and dosing. This review looks at the value of pre-treatment anti-Mullerian hormone (AMH) value in choosing the appropriate modality of treatment and its predictive ability for the outcomes of such treatment. It briefly addresses the factors that may modulate AMH levels and make clinical decision-making challenging.

Keywords: *Anti-Mullerian hormone, clinical utility of anti-Mullerian hormone, in vitro fertilisation, ovulation induction, polycystic ovary syndrome*

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility in women with PCOS.[1,2] Anti-Mullerian hormone (AMH) is an ovarian growth factor exclusively produced by the granulosa cells of the ovarian follicle.[3-5] Circulating concentration of AMH shows a 2–3-fold increase in women with PCOS compared to normo-ovulatory women.[6-8] Both increased number of follicles and increased secretion from individual cells contribute to its high serum concentration in PCOS.[9,10] The Rotterdam consensus is the most widely utilised criteria for the diagnosis of PCOS which includes the ultrasound parameter of excess antral follicles or polycystic ovarian morphology (PCOM) as one of its components.[11] AMH has long been proposed as an alternative for PCOM as a diagnostic criterion. The most recent updated evidence-based guidelines recommend that serum AMH could be used for defining PCOM in adults for the diagnosis of PCOS in combination with other criteria.[12]

AMH has an inhibitory effect on early follicular recruitment, preventing the primordial follicles from entering the growing follicular pool and premature exhaustion of the primordial pool.[13-15] In addition, AMH reduces follicle sensitivity to follicle-stimulating hormone (FSH) and thus inhibits cyclical follicle recruitment.[16] Understanding the ovarian follicle physiology provides an opportunity to extend the role of AMH in the management of PCOS beyond diagnosis alone.[17] The assay methodology for the measurement of AMH has evolved over the past two decades. Initial semi-automated assays with different antibodies have posed various challenges, despite providing an important understanding of ovarian reserve. These included assay stability under various conditions and interpretation and comparison of AMH values from different assays, thus limiting our ability to understand the clinical utility of AMH in various clinical situations. However, the availability of fully automated tests and attempts at harmonisation of AMH assays have reduced the magnitude of this problem in recent years.[18] This review discusses the important role the analyte plays in decision-making, beyond a reflection of ovarian reserve during the management of infertile women with PCOS.

Materials and Methods

Literature search was performed in PubMed, Medline and Google Scholar until August 2023, using the terms: PCOS, anti-Mullerian Hormone, AMH and clinical utility of AMH. Randomised controlled trials

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Address for correspondence: Dr. Padma Rekha Jirge, Sushrut Assisted Conception Clinic, Shreyas Hospital, 2013e, 6th Lane, Rajarampuri, Kolhapur, India.
E-mail: rekha.jirge@gmail.com

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and observational studies published in English were included. Case series, case reports and non-English language publications were excluded. Cross-references were manually searched. Zotero was used for reference management. Figure 1 shows the details of the search strategy.

Anti-Mullerian Hormone and its Role in Clinical Decision-making in Polycystic Ovary Syndrome-related Infertility

The following section provides a comprehensive insight into the role of AMH in decision-making before various treatment modalities for infertility in women with PCOS. In addition, it summarises the factors that may modulate AMH levels and hence pose additional challenges in clinical interpretation.

Anti-Mullerian hormone and *in vitro* fertilisation

The most established role of AMH in treatment planning is in the context of *in vitro* fertilisation (IVF). It predicts hyper-response with the highest sensitivity and specificity.[19,20] Women with PCOS are at a high risk of developing ovarian hyperstimulation syndrome (OHSS) while undergoing IVF. Even though titrating the dose of gonadotropin may be challenging in a small proportion of them, a prior knowledge of AMH levels offers a very important opportunity to improve the safety of treatment in the majority.[21] Initial reports using the Diagnostic Systems Laboratories (DSL) assay reported that values above 3.5 ng/l predict excessive response with 88% sensitivity and 70% specificity.[20] A low starting dose of gonadotropin, preference for antagonist protocol and choosing GnRH agonist over human chorionic gonadotropin for oocyte maturation in those with high response are all the strategies that minimise the risk of hyper-response and consequent OHSS in women with PCOS.[22-26]

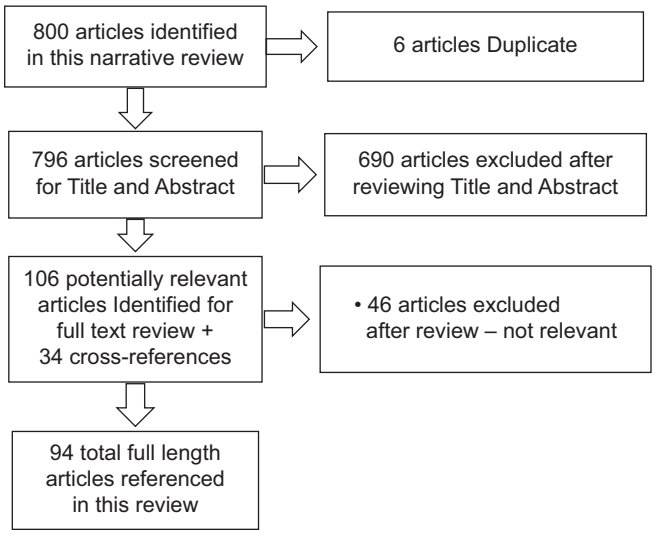

Figure 1: PRISMA flow chart of search strategy

The role of AMH as a predictor of success in IVF in addition to ovarian response has been explored during the past decade. Considering its strong correlation with ovarian response, it might be expected that a high AMH is predictive of an increased live birth rate (LBR). There is evidence, even though inconclusive, to suggest that AMH is a predictor of live birth in IVF.[24,27-29] An improved live birth is noted with increasing AMH in an unselected population which is attributed to the strong correlation between AMH and oocyte yield.[24] The association between AMH and ART outcomes appears to remain despite correcting for age and is more apparent in older women.[30,31] The first meta-analysis addressing the association between live birth and AMH general population of women undergoing IVF reported a weak predictive value of AMH for LBR with IVF and recommended utilising the information for counselling couples before IVF.[28] With changing clinical practice and segmentation of IVF cycles, cumulative LBR (cLBR) is a more meaningful measure for the success of IVF, and AMH shows a weak positive predictive value for cLBR as well.[29]

A prospective study reported a positive correlation between AMH on day 3 of an IVF cycle and implantation and pregnancy rate in women with PCOS. However, the results of this study should be interpreted with caution both due to the criteria used to define PCOS and the AMH levels in the study population. Using the DSL assay, the AMH value at the 75th centile of the study group was relatively low at 3.85 ng/ml, which could be the result of the chosen study population.[32] A further systematic review reported a weaker link between implantation or clinical pregnancy and PCOS compared to those with unspecified ovarian reserve.[33] In addition to the ovarian reserve, factors such as severity of the condition and associated metabolic and endocrine alterations influence the serum values of AMH in PCOS.[34-36] Increased number of follicles and variable increase in the secretion from individual follicles are additional confounders.[9,10,37] Any or all of these factors may be contributing to the AMH levels in PCOS and prevent a better understanding of its correlation to clinical outcomes in IVF. However, a high serum AMH concentration can be a useful guide for a positive pre-treatment counselling in young infertile women.

There is concern that women with PCOS with very high AMH (variedly defined as >8.27 ng/ml or >12 ng/ml) may have a lower LBR compared to those with lower levels.[38,39] Various factors have been postulated to be contributing to this problem. Oocyte quality and

endometrial aberrations could be two of the important contributors to this not yet fully understood paradox.[40-43] Different phenotypes and their underlying endocrine abnormalities are other factors which may influence LBR.[38,44,45] However, data from the Society for Assisted Reproductive Technology registry involving more than 2700 patients with PCOS suggest no decline in LBR per completed embryo transfer and attribute the decline in LBR following fresh cycles in women with PCOS to cycle cancellation and segmentation.[46] An analysis of LBR in fresh transfers in women with AMH values of ≥5 ng/ml showed a 3% decrease in the odds of live birth in fresh autologous IVF, with each unit increase in AMH. However, this was due to an increased incidence of fresh embryo transfer cancellation because of concerns regarding OHSS.[46] Hence, AMH plays an important role in pre-treatment counselling of those with very high levels, to alert them to an increased possibility of segmentation of treatment and subsequent frozen embryo transfer.

Anti-Mullerian hormone and ovulation induction

Oral ovulation-inducing agents are the first line of treatment for PCOS-related infertility.

Although letrozole (LET) is now considered the first choice for such a treatment,[12,47,48] clomiphene citrate (CC) continues to be used as an alternative first-line agent for ovulation induction (OI) in PCOS. Clomiphene resistance, seen in up to 25% of women with PCOS and infertility, is diagnosed only after unsuccessful OI with incremental doses of CC in successive cycles.[49] It is important to note that AMH values above 7.7 ng/ml predict a low chance of successful ovulation with CC. Importantly, higher levels of AMH do not predict non-responsiveness to gonadotropins.[50]

A subsequent study reported that an AMH level above 3.4 ng/ml may identify women likely to be resistant to OI.[51] The use of Immunotech (IOT) assays in the initial studies and Uscan in the latter study is attributed to such different discriminatory values of AMH. This also highlights the challenges encountered with different AMH assays in the absence of international standardisation or harmonisation. IOT is considered to yield higher values than Uscan or DSL assays. Another study using AMH Gen II assay found a level of 8.58 ng/ml to have 78% sensitivity and 67% specificity for the prediction of non-response to CC.[52] A small retrospective study further reported an AMH level of 9.78 as the discriminatory level beyond which cumulative ovulation rates were significantly lower.[53] Finally, in a large cohort study of women with PCOS using Gen II AMH assay, it was noted that women with higher AMH levels needed higher doses of CC or LET to achieve ovulation and the chances of ovulation reduced with increasing levels of AMH.[54] *In vitro* studies involving human granulosa cells suggest that the probable underlying mechanism is related to high AMH, as high AMH inhibits aromatase activity and reduces follicular sensitivity to FSH.[55-57] Despite the challenges in inter-assay comparison, it is important to note that anovulatory women with PCOS with very high serum AMH values are less likely to ovulate with CC or LET. Incorporating this into treatment planning can avoid protracted treatment cycles without ovulation and the frustration patients experience thereof.

Anti-Mullerian hormone and intrauterine insemination

There have been some efforts to evaluate whether AMH has any predictive role in intrauterine insemination (IUI). Data from a large retrospective study including more than 700 cycles of IUI show that those with high AMH were less likely to respond to CC or LET, particularly at levels >9.3 ng/ml. Further, this observation was more pronounced with CC compared to LE. However, such an issue was not encountered with exogenous gonadotropin.[58] The authors suggest that in the subgroup of women with very high AMH, gonadotropin may be considered a first-line therapy or alternatively a high starting dose of CC or LE can be considered.[58]

Interestingly, a pilot study evaluating pre-treatment AMH levels in gonadotropin cycles shows a good response in those with AMH ≤4.7 ng/ml. The authors documented a poor response in those above 10.2 ng/ml.[59] This may be a reflection of a very high number of small follicles in such women contributing to excessive AMH levels, which consequently adversely influence the follicular sensitivity to FSH and hence reduced response to exogenous gonadotropins.[9,19,56,59] In addition, ovarian stimulation strategies for IUI are milder than those used in the context of IVF to avoid the risk of high-order multiple pregnancies or OHSS. Currently, there is no evidence evaluating any correlation between AMH values and LBR after IUI.

Anti-Mullerian hormone and *in vitro* maturation

It is well known that a subset of women undergoing IVF is at considerably high risk of developing OHSS with gonadotropin stimulation. *In vitro* maturation (IVM) is considered a safer option in them as currently IVM is the only strategy with no reported cases of OHSS.[60] Despite its availability since 1935[61] and recent improvements in clinical and laboratory protocols, its acceptance is limited due to lower pregnancy rates compared to conventional IVF.[62,63]

A predictive model utilising AMH and antral follicle count (AFC) has been recommended to choose appropriate candidates for and optimise ovarian response in IVM.[60] An AMH level of 1.63 ng/ml using DSL assay can predict the chances of obtaining five mature oocytes following IVM with a sensitivity of 81% and a specificity of 53%.[64] Further, in women with PCOS, collection of at least eight COCs has been associated with a higher cumulative pregnancy rate. Very high AMH (14.8 ± 10.1 ng/ml) using IOT assay and AFC (38.6 ± 16.1) may have a strong predictive potential (area under the curve = 0.7864) for the number of COCs retrieved. In another cohort study, an AMH level of 8.5 ng/ml or higher was associated with PR comparable to IVF.[65] While the different assays used for AMH may limit the interpretation of the results, a brief description is provided in the discussion section which may be of help in understanding the evolution and interpretation of AMH assays.

Anti-Mullerian hormone and metabolic abnormalities

The negative impact of abnormal metabolic health on maternal and foetal health during pregnancy is increasingly being understood. The prognostic role of AMH has been evaluated in women with PCOS to predict the probability of metabolic syndrome (MetS). The current evidence is limited, conflicting and does not support a prognostic role for AMH in women with PCOS to predict an increased risk of MetS.[66-68]

Anti-Mullerian hormone and preterm delivery

Elevated AMH has been reported as a risk factor for an increased incidence of preterm delivery (PTD) in women with PCOS treated for infertility. This appears to be independent from any of its associations with insulin resistance or hyperandrogenemia.[69-72] There is a need for an increased understanding of this underlying association and awareness of such a risk amongst clinicians providing antenatal care to such women.

Factors modulating anti-Mullerian hormone concentrations

The previous section addresses the important role of AMH in the management of PCOS beyond its diagnosis. However, it is important to consider the common factors which may modulate its values and consequently interfere with its interpretation. The detrimental effect of smoking on ovarian reserve has been previously documented.[73] However, its effect on AMH in PCOS if any has not been documented and hence will not be discussed here. Table 1 summarises the current evidence on the factors that may modulate AMH levels in women with PCOS considering or undergoing treatment for infertility.

Table 1: Factors with modulatory effect on anti-Mullerian hormone levels in infertile women with polycystic ovary syndrome

Factors	Effect on AMH	Comments
Age	Declines with age	-
LOD	Declines (normalises)	-
Metformin	Declines	-
COCP	Declines	Effect seen within 1–3 months of initiating treatment
Vitamin D	Effect inconclusive	Current data – inconclusive of the direction of the effect
Genital TB	Declines	-
Obesity	Declines	Levels remain above non-PCOS

AMH=Anti-Mullerian hormone, PCOS=Polycystic ovary syndrome, LOD=Laparoscopic ovarian drilling, COCP=Combined oral contraceptive pill, TB=Tuberculosis

Age

Ovarian reserve declines with age and is associated with a decline in pregnancy and livebirth rates in older women.[74] Diagnosis of PCOS may be challenging in older women with lower AMH values compared to younger women. However, a serum AMH above the 75th percentile for age is highly suggestive of PCOS.[75] This criterion would be relevant where population nomogram exists.

There is evidence that the pregnancy rate does not differ in women with different AMH values, in an unselected population of women below the age of 34 years undergoing IVF. However, in older women above 42 years of age, a high AMH does not improve the pregnancy rate underscoring the importance of qualitative decline in oocytes with age.[31] Further, despite a higher oocyte yield, PCOS women do not appear to have an extended reproductive window.[76,77] Hence, AMH may not retain its predictive value for cLBR in older women.

Laparoscopic ovarian drilling

Laparoscopic ovarian drilling (LOD) is considered a second-line therapy for PCOS-related infertility.[12,78] A recent meta-analysis shows a decline in AMH values after LOD, and the results are consistent despite different durations of reported follow-up, different assay kits for AMH used, whether the procedure was performed on both or single ovary and the type of energy used.[79] It is considered normalisation of ovarian reserve rather than any real damage to the ovarian reserve. A reduced AMH following LOD may predict a lowered risk of OHSS in any subsequent IVF and reduced multiple pregnancy following OI in women with PCOS.[80]

Obesity

There is conflicting evidence on the impact of obesity in PCOS on serum AMH values. Obese PCOS women have

lower levels of AMH but still higher than non-PCOS women.[74,81] A recent report suggests a lower AMH level in young PCOS with increased cardiometabolic risk, and every unit reduction may indicate a 10% increased risk of MetS.[66]

Pharmacological agents and bariatric surgery play an important role in managing morbid obesity associated with PCOS and contribute towards improved fertility in such women.

The use of sibutramine in PCOS women, while achieving weight loss, leads to a decrease in AMH level which is hypothesised to be due to its direct ovarian action on the endocannabinoid system in the ovary.[82] It is interesting to note that a combination of diet, physical activity and pharmacological (orlistat) induced weight loss in overweight and obese PCOS women leads to improved metabolic status, HA and an increased AMH.[83] A similar increase is noted following sleeve gastrectomy as well.[84] Hence, treatment modality needs to be taken into consideration while interpreting AMH values following any treatment of obesity for an appropriate decision-making.

Medications

Metformin co-treatment is often an integral part of the management of PCOS-related infertility. A recent meta-analysis shows that obese women who are on metformin for more than 2 months may experience a 30% decline in AMH and this decline could be more pronounced in lean PCOS women.[85]

Oral contraceptive pills (OCPs) are often used in women with PCOS to treat certain endocrine abnormalities before active fertility treatment. AMH is reduced in current OCP users, and the decline is experienced in <3 months of use and can be as high as 60%–70% in both non-PCOS and PCOS women.[85,86] Hence, decision-making based on AMH values in current or recent OCP users may be affected.

Vitamin D3 deficiency

While there appears to be a cause–effect relationship between Vitamin D levels and AMH, the current evidence is inconclusive regarding the direction of effect either for its deficiency or for supplementation on serum AMH values.[87-89]

Genital infections

Genital tuberculosis (GTB) is a common cause of infertility and may co-exist with PCOS.[90] It is known that GTB is associated with reduced ovarian reserve.[90,91] It is to be noted that both PCOS and GTB are prevalent in many of the low- and middle-income countries and such co-existence may mask the diagnosis of PCOS. In addition, it may also affect the clinical utility of AMH for treatment planning and add to failures of treatment.

Discussion

This review provides a comprehensive insight into the prognostic role of AMH while strategising various treatments in infertile women with PCOS. It is well known that AMH is a robust alternative for PCOM in the diagnosis of PCOS. However, it should be used in conjunction with either oligo-ovulation or clinical/biochemical hyperandrogenism to arrive at the diagnosis.[12] The role of this powerful analyte is not limited to the estimation of ovarian reserve alone, and the current evidence shows its ability to influence treatment decisions in PCOS-related infertility. The evidence supports its prognostic role in addition to the endocrine or metabolic markers commonly seen in PCOS.[92] Translating this insight into clinical practice offers an opportunity for effective pre-treatment counselling and planning. It may help avoid protracted courses of medications and timely recourse to effective treatment strategies with added emotional and financial benefits. Hence, the most important role of AMH in PCOS-related infertility is its clinical utility as a predictive and prognostic tool. Majority of the women with PCOS conceive with simple interventions, and awareness of pre-treatment AMH values will help in deciding the choice of treatment modality.

A high pre-treatment AMH merits initiating OI with higher doses of CC or LET than used in ovulatory women.[50-54] Alternatively, gonadotropins may be more effective in inducing ovulation in such women. In the context of IUI, very high levels of AMH >10 ng/ml may predict a poor response even with gonadotropins.[59] The prognostic role of AMH in predicting ovarian response in IVF is well established. This has led to the adoption of individualised controlled ovarian stimulation strategies which have improved the safety of IVF in PCOS by reducing the incidence of significant OHSS.[26] AMH may also guide in decision-making and identify women in whom IVM may be a safer option than IVF without compromising pregnancy rates.[64,65] In addition, AMH has a weak predictive ability for LBR except in women with advanced maternal age. Another predictive role of AMH that is not widely acknowledged is its ability to predict an increased risk of PTD in women with high AMH who conceive following treatment for PCOS-related infertility.[69-72] It is important to incorporate the impact of any factors that may modulate the AMH values into the decision-making process.

An important and ongoing challenge in AMH estimation, which has prevented comparison between clinics or

populations and thus limited the clinical utility, has been the laboratory issues with various assays used. The initial assays including DSL, IOT and Gen II utilise enzyme-linked immunosorbent assay (ELISA) methodology. The use of different antibodies, the differential effect of various sample storage and processing on results, lack of internationally standardised material for uniform calibration and lack of awareness of the differential performance of various assays have all limited the clinical utility of AMH.[93] There are no universally accepted values of conversion factors for inter-assay comparison. Similar issues exist with the currently available tests of ultrasensitive ELISA (Ansh) or fully automated chemi-immunoluminiscene (Elecsys and Access), which has prevented harmonisation of results.[18,94] Access assay-measured values of AMH may be 5%–15% higher than Elecsys.[18] This has important clinical implications including wrong dosing and compromised safety of treatment. Sample storage and batch processing is a common practice in clinical laboratories. With all the three assays currently available, there is a difference in the AMH values obtained between the fresh and the frozen-thawed serum samples.[95] Both Elecsys and Access AMH assays show a very small decrease in the AMH value in frozen-thawed samples in comparison to fresh samples, considered to be of little clinical importance. Contrarily, higher values are noted in the frozen-thawed samples compared to the fresh samples with ultrasensitive ELISA (Ansh) assay, and the magnitude of difference may be of clinical importance.[95] This is another factor to be considered while incorporating AMH values for clinical decision-making.

Conclusion

The role of AMH as a quantitative marker of ovarian reserve has long been established. This review looks at its value beyond the diagnostic role towards its predictive and prognostic role in various treatment options available for infertile women with PCOS. Current evidence does not support AMH as an additional diagnostic marker in those with an established diagnosis of PCOS or its evaluation routinely before the first-line therapy of oral OI. However, AMH may play an important role and assist in clinical decision-making in those resistant to or fail to conceive with oral ovulogens, to avoid protracted treatment cycles. Laboratory issues related to different AMH assays have been a limiting factor in understanding and utilising this powerful analyte to the fullest extent. An awareness of the clinical scenarios that may influence the AMH values is important for the effective use of this tool in decision-making and treatment planning.

Author's contributions

DS – Concept, manuscript preparation, editing and review. PRJ – Concept, literature search, manuscript preparation, editing and review.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

No original data used.

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