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Review

Measuring anti-Müllerian hormone for the assessment of ovarian reserve: When and for whom is it indicated?

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ABSTRACT

Our understanding of female reproductive function has been hampered by our inability to directly assess the number of non-growing primordial follicles present in the ovary, the ovarian reserve. Female reproductive hormones (FSH and LH, the inhibins and steroids) reflect the activity of the larger growing follicles and thus are largely informative of peri-ovulatory ovarian activity. In contrast anti-Müllerian hormone (AMH) is a product of the granulosa cells of small growing follicles, whose number (and therefore circulating AMH concentrations) is reflective of the ovarian reserve. AMH declines with age in adult women, and emerging data suggest a relationship with remaining reproductive lifespan and age at the menopause. Early studies demonstrated that AMH concentrations are stable across the menstrual cycle, adding to its clinical utility. The most established role for AMH measurement is in women about to start IVF treatment, where it is predictive of the ovarian response and is of clear value in identifying women at risk of ovarian hyperstimulation syndrome or whose response will be poor and thus their expectations can be tailored. AMH is detectable in childhood, and although relationships to puberty are not yet available, it appears that AMH rises to a peak in the early 20s. Developing indications include in assessment and individualisation of the risk to fertility from chemotherapy, in the diagnosis of PCOS and as a tumour marker in granulosa cell tumours. The increasingly routine use of AMH by IVF clinics heralds much wider adoption in a range of clinical situations across the reproductive lifespan.

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1. Introduction

Our current understanding of female reproductive function presumes that the ovary contains a finite number of oocytes within primordial follicles, and that their depletion heralds the menopause [1]. This pool of primordial follicles is formed during fetal life from approximately 18 weeks gestation, following oogonial proliferation, entry and arrest in meiosis, and interaction with somatic cells. A small number of this resting pool of primordial follicles is activated into growth every day throughout the reproductive lifespan of a woman (including in childhood) with the vast majority destined to undergo atresia [2]. Indeed before puberty all growing follicles will become atretic, and after puberty only one a month may escape this fate and progress to ovulation. The pool of resting follicles is the true ovarian reserve, but the term ‘ovarian reserve’ is also widely used in the assisted conception literature to mean the number of growing follicles that can be recruited by exogenous FSH to grow to a pre-ovulatory stage, resulting in the potential collection of an oocyte for assisted reproduction. This growing pool is perhaps better termed the functional ovarian reserve. Although the true and functional ovarian reserves reflect different stages of follicular development, they are inherently linked and both decline in parallel with increasing age. Accurate measurement of the ovarian reserve has long been a quest in reproductive medicine and recent years have seen a dramatic increase in research in this field, a large part of which has been fuelled by the recognition that measurement of anti-Müllerian hormone (AMH) in serum is a much more accurate measure of the ovarian reserve than the other hormones that have previously been available to us. Thus while inhibin B shows good prediction of oocyte yield after superovulation [3], it requires measurement in the early follicular phase of the menstrual cycle and only decreases late in the reproductive years [4]. It has therefore not supplanted FSH as the most widely used marker of the ovarian reserve despite the latter hormone’s well-recognised limitations.

AMH was first identified in the 1940s on the basis of its production by the fetal Sertoli cell, resulting in loss of the Müllerian duct system in the male. Production of AMH by granulosa cells in the adult ovary was first reported 30 years ago, in the chicken [5], but research into its function and clinical utility only gathered pace at the turn of the century with the development of commercially available assays. Early studies demonstrated that serum AMH showed a close correlation with the number of oocytes that were obtained following superovulation for IVF [6], and that it declined with age in women [7,8]. These two findings are central to our current understanding of the utility of AMH as a measure of the ovarian reserve.

In contrast to the large amount of clinical research on the utility of measuring AMH, there are remarkably few data regarding its biological functions. Early studies using an AMH knock-out mouse demonstrated that perhaps its most important role is the regulation of initiation of early follicle growth [9,10], and subsequent studies have indicated that it may regulate the responsiveness of growing follicles to FSH [11]. AMH production by cumulus cells is stimulated by the oocyte [12] consistent with additional functions in mediating oocyte/cumulus maturation. In keeping with these roles, AMH expression by granulosa cells of the follicle is initiated at the onset of follicle growth, but equally importantly expression then declines rapidly with little expression in antral follicles beyond 6–8 mm diameter in the human [13]. The lack of production of AMH by the mural granulosa of larger follicles in the lead up to ovulation (or by the corpus luteum) is critical for its clinical utility as it means that its serum concentration varies little over the menstrual cycle [14,15]. Thus for practical purposes it can be assayed at any stage of the cycle.

Recognition of these unique characteristics has led to the rapid adoption of AMH for a range of indications. In this review we discuss the potential uses and recent developments for AMH, and summarise the evidence supporting its adoption into clinical practice.

1.1. Assessment of ovarian reserve before assisted conception

This is the most established indication for measuring AMH, with many clinics now routinely assaying AMH before IVF treatment. As AMH correlates strongly with the number of oocytes obtained following superovulation, a baseline measurement allows individualisation of both the treatment strategy and the patient’s expectations [16,17]. Specifically women with a high AMH are likely to respond excessively to exogenous gonadotrophins and their treatment strategy can be modified to minimise the risk of ovarian hyperstimulation syndrome (OHSS). Conversely women with a low AMH are likely to respond poorly to stimulation with consequently a low chance of pregnancy, and their expectations can be managed appropriately with alternatives like oocyte donation discussed. Although AMH is primarily a measure of oocyte quantity rather than quality, it is positively associated with IVF live birth rates independently of age [16,18,19]. This is primarily due to its relationship with oocyte yield, as at any given age range women with a higher AMH are likely to have more oocytes retrieved and thereby potentially more embryos for selection.

The cost-effectiveness of the use of an AMH-based treatment strategy in IVF has recently been assessed, and proposed to lead to substantial savings [20]. Some of this is through the more accurate identification of women at risk of OHSS who can then be treated with a less intense stimulation regimen, with significant cost savings from fewer hospital admissions for OHSS. A less patient-centred aspect of this analysis was however the exclusion of women with a very low AMH from state funded IVF, which will inevitably result in exclusion of some women with a low-but not zero-chance of success as there is no AMH concentration, even when it is undetectable, that is associated with absolutely no chance of pregnancy.

1.2. Age-specific interpretation of AMH as a surrogate measure of ovarian reserve

The production of AMH by the growing follicle pool means that its concentration varies across childhood, adolescence and adult life [7,21]. Initial adult cohorts clearly demonstrated an age related decline reaching undetectable levels in advance of the menopause [22]. Subsequently AMH nomograms have been reported and validated from very large cohorts of women [23–25]. While these data derive from women attending infertility clinics, subset analysis of women where there was a severe male contribution to the infertility (and where female pathology is therefore less likely) showed no difference from the whole cohort. Longitudinal data are lacking, but the size of the cross-sectional cohorts now reported make it likely that they will indeed reflect longitudinal changes at a population level.

More recently AMH concentrations in populations of children and younger adults have been described, and a compilation of these data now allows a description of AMH concentration from birth to the menopause (Fig. 1) [26]. This confirms a transient neonatal rise in AMH similar to the well-described mini-puberty of the male neonate, with a subsequent rise through childhood and adolescence to a peak in the early 20s. Concentrations then decline from the late 20s. Collectively these data indicate that AMH shows no dramatic change at puberty but shows an increase from late childhood through to early adulthood. These data are derived from cross-sectional analyses and prospective multiple sampling through puberty is required to test and refine this model. The

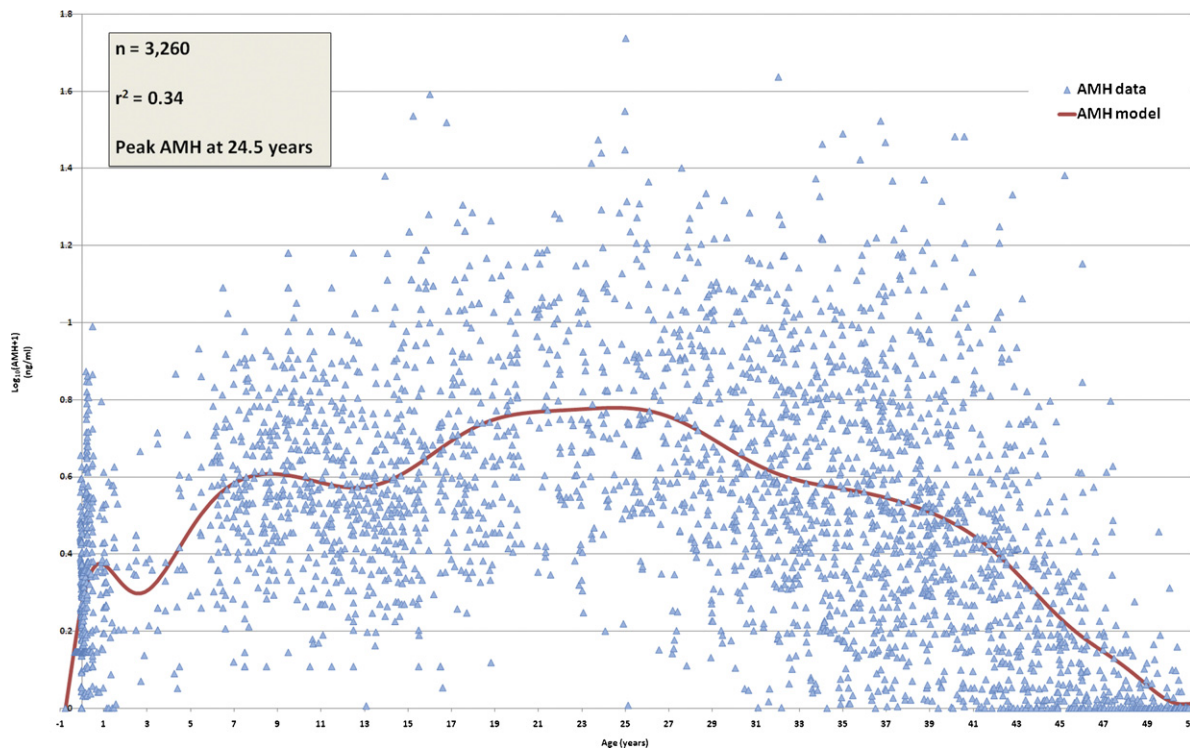


Fig. 1. Serum AMH from conception to the menopause (note log scale). The red line is the peak model that best fits the 3260 datapoints shown as triangles. The coefficient of determination, r^2 , is 0.34, indicating that 34% of variation in serum AMH levels is due to age alone. Peak serum AMH is at 24.5 years.

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continuing rise through later adolescence suggests that there are ongoing changes in patterns of follicle maturation over perhaps a decade following menarche.

These large studies also confirm the wide variability in AMH between women. This is in fact to be expected, as there is a comparably wide range in primordial and non-growing follicle number [1,27], and in age at menopause. The age-related changes in AMH have also been modelled relative to the non-growing follicle (NGF) pool [28]. During childhood the NGF shows an inverse relationship with AMH (i.e. the former is declining while the latter is rising), but both AMH and the rate of loss of the NGF pool (assumed to reflect largely initiation of follicle growth) rise in parallel. After a peak at age 24, both AMH and NGF activation rate both start to fall, mirroring the fall in non-growing follicle numbers.

1.3. Assessing and predicting gonadal damage

Our ability to interpret AMH in an age-specific manner has allowed the development of new applications. These include accurate assessment of the impact of gonadotoxic therapy, e.g. chemotherapy and radiotherapy, or of ovarian surgery, on the ovarian reserve [29,30]. AMH falls very rapidly with the onset of chemotherapy [31,32]. In lymphoma analysis allowed the clear demonstration of the toxicity of alkylating agent based therapy, as those women showed little or no recovery of AMH following chemotherapy, whereas women receiving non-alkylating agent therapy showed a good recovery to approximately pre-treatment concentrations [32]. AMH is also useful in prepubertal girls, showing a fall during chemotherapy with recovery dependant on the toxicity of the regimen used [33], while other reproductive hormones are not of value in this context. Post-treatment follow-up studies have also shown that AMH concentrations are reduced in women following treatment for cancer, either in childhood or adulthood, with low AMH concentrations most consistently seen

following total body radiation [31,34–37]. Normal concentrations have also been reported in populations of women following certain chemotherapy regimens indicating that those particular therapies do not cause loss of the ovarian reserve that is detectable using this marker [37,38]. This essentially reassuring result in some women requires long term follow up with both fertility and age of menopause as endpoints, and at present data with that degree of completeness are lacking. The ability of the reproductive system to compensate for rapid loss of follicle number is indicated by the only modest change in reproductive lifespan following unilateral oophorectomy [39]. If translatable to the post-chemotherapy situation, this might indicate that only very substantial loss of the ovarian reserve will have a clinically relevant impact. As AMH reflects the number of growing follicles, small changes in the rate of activation may well not be detectable.

Comparable results have been reported following surgery for ovarian endometriosis [30], with a fall in AMH immediately following surgery, and recovery thereafter. Assuming that primordial follicles cannot be replaced and that surgery (and chemotherapy) removes both growing and non-growing follicles, this can only indicate that a smaller non-growing pool re-establishes a similar growing pool to that present pretreatment, thus normalising AMH. It would appear, however, reasonable to reassure a woman regarding future fertility prospects if her AMH is normal following recovery from cancer or other treatments although there is a lack of prospective data to substantiate this fully at present.

A further consideration is whether a higher pre-treatment AMH before chemotherapy makes it more likely that a woman will retain ovarian function following treatment, whereas a woman of the same age but with a lower AMH is more at risk of experiencing a premature menopause. In support of this initial studies demonstrated that pre-treatment AMH was higher in women treated for breast cancer who retained menses 1 year after chemotherapy

[40], and with higher post-treatment AMH concentrations [41], although others have found no difference [42]. A recent analysis of menstrual and ovarian function 5 years after chemotherapy for breast cancer found that pretreatment AMH was indeed a predictor of ongoing menses (with associated biochemical evidence of increased ovarian activity) at that time [43]. Age was also a predictor, as expected, but strikingly in a multivariate analysis only AMH remained predictive, with the effect of age no longer significant. This is consistent with age being a surrogate marker of the ovarian reserve whose value becomes redundant when a direct marker of adequate accuracy is included. This finding has since been replicated in a preliminary report of a further small cohort [44], but should also be replicated in younger cohorts of women with other conditions, e.g. lymphoma, before this test can be recommended for clinical practice. Furthermore it should be recognised that these studies used ovarian function rather than fertility as an outcome and while this is relevant for some long-term outcomes such as osteoporosis and other risks of early ovarian insufficiency, for many women the key question will be whether they will retain their fertility after chemotherapy. Confirmation that AMH provides individualisation of risk can rapidly translate into clinical practice, with more invasive or time-consuming methods of fertility preservation being appropriate for women with a low AMH whereas others with a high AMH may elect to start treatment without delay.

1.4. *Diagnosis in oligo/amenorrhea*

Although we have classically measured gonadotrophins and oestradiol to subclassify oligoamenorrhoea, a single AMH measurement may be a better first line investigation. In oligoamenorrhoeic women with Polycystic Ovarian Syndrome (PCOS), AMH is often dramatically high due to AMH being produced by the large number of antral follicles [45,46]. Conversely women with amenorrhoea due to premature ovarian insufficiency have a low AMH, while women with amenorrhea related to hyperprolactinemia or in hypogonadotrophic hypogonadism often have normal circulating concentrations of AMH [47]. AMH is also very high in women with granulosa cell tumours, where it is of value as a tumour marker [48].

Women with hyperprolactinemia or hypogonadotrophic hypogonadism will have low FSH concentrations and this might therefore be expected to reduce AMH production from the growing follicle pool. However the degree of gonadotropin suppression seems to be largely insufficient to influence AMH production in these two groups of women. Likewise AMH production is reported to be unaffected in women taking the combined contraceptive pill who also have significant gonadotropin suppression [49], although a rise in AMH following discontinuation of the contraceptive pill has also been reported [50]. It appears that more prolonged and complete gonadotropin suppression can cause more readily detectable suppression of AMH, as seen in women on long-term goserelin treatment for breast cancer [31], and this may also underpin the decline in AMH concentrations during pregnancy [51]. Clinical experience indicates that some women with hypogonadotrophic hypogonadism do have a low AMH, and further well-defined cohorts of women with this condition (including follow up to recovery of normal ovarian function) are needed to delineate in detail possible changes in AMH. AMH is thus far not part of the diagnostic work up for PCOS but the criteria for making this diagnosis remains subject to revision and it may well be that AMH becomes part of this in due course [52]. Certainly the markedly elevated AMH concentrations contrast to the frequently normal values of other reproductive hormones in PCOS, thus raising the possibility of a clear biochemical aspect to the diagnosis, which can also only aid further our understanding of this condition.

1.5. *Prediction of reproductive lifespan*

The decline in AMH during the later reproductive years is one of the most established findings, in both prospective and cross-sectional studies, thus raising the possibility of prediction of the menopause [22] and by implication, a woman's remaining reproductive lifespan. In analysis of serial blood samples taken from 50 women followed prospectively from the age of 42 it was demonstrated that AMH declined to undetectable levels some 5 years before the final menstrual period (FMP) [53]. Inhibin B declined similarly becoming undetectable some 4 years before the FMP. AMH was significantly related both to time to and age at FMP, whereas inhibin B was less predictive of both. A recent larger Dutch study has provided further evidence that AMH could provide long-term prediction of age at menopause [54]. The study included 257 ovulatory women aged 21–46, who were reassessed after 11 years. Analysis showed that a low age-specific AMH at initial testing was associated with a shift in the distribution of the menopause to a younger age, whereas a higher age-specific AMH shifted the distribution toward a higher age. Importantly in this study the use of AMH was in the context of age, rather than independent of it. Even in this fairly large study however only some 11% of the women studied had become menopausal during the follow up period and thus larger and longer duration studies will be required to provide accurate estimates of the predictive power of AMH and the variability associated with this. It must be recognised that age at menopause is very strongly genetically determined and although a large number of environmental influences have been identified, their combined effect is modest [55]. It will be interesting in future work to assess whether AMH is a better predictor than knowing the mothers' age at menopause.

2. Conclusion

The last decade has provided a wealth of data confirming the value of AMH as a measure of the ovarian reserve. The clearest data for its clinical utility is in the context of IVF and measurement has been routine practice in some clinics now for several years. The validity of the evidence base for other indications is weaker but rapidly growing. Much of the value of AMH lies in its relation to the declining ovarian pool with age, and thus its potential ability to predict future reproductive outcomes. We must again emphasise how little longitudinal or prospective data there are in this field and therefore its clinical use in advising individual women outside the context of IVF is not well supported. The use of AMH in women with a new cancer diagnosis is promising as it may allow greater individualisation of risk than is currently available, and its value in the differential diagnosis of oligoamenorrhoea seems clear. It is inevitable that AMH will be increasingly measured by women wishing to know their future reproductive lifespan, as societal changes will continue to result in women increasingly delaying childbearing until their later reproductive years. This is likely to go hand in hand with the more widespread use of fertility preservation technologies such as oocyte vitrification for non-medical reasons despite the lack of a clear evidence base. While bearing these caveats in mind it is clear that the increasing use of AMH will be of substantial benefit widely across reproductive medicine.

Contributors

Professor Richard A. Anderson contributed in writing of ms, approval of final version. Professor W. Hamish B. Wallace contributed in writing of ms, approval of final version. Professor Scott M. Nelson contributed in writing of ms, approval of final version.

Competing interests

R.A. Anderson and S.M. Nelson have acted as consultants for Beckman Coulter and Roche Diagnostics.

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