PUBLISHED SCIENTIFIC EVIDENCE ON THE USE OF ANTI-MÜLLERIAN HORMONE

Anti-Müllerian Hormone (AMH)
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"The use of Beckman Coulter’s AMH assay has revolutionized approaches to controlled ovarian stimulation."

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Anti-Müllerian hormone-based prediction model for a live birth in assisted reproduction.

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Abstract
BACKGROUND: Prediction of assisted reproduction treatment outcome has been the focus of clinical research for many years, with a variety of prognostic models describing the probability of an ongoing pregnancy or a live birth. This study assessed whether serum anti-Müllerian hormone (AMH) concentrations may be incorporated into a model to enhance the prediction of a live birth in women undergoing their first IVF cycle, by analyzing a database containing clinical and laboratory information on IVF cycles carried out between 2005 and 2008 at the Mother–Infant Department of University Hospital, Modena. Logistic regression was used to examine the association of live birth with baseline patient characteristics. Only AMH and age were demonstrated in regression analysis to predict live birth, so a model solely based on these two criteria was generated. The model permitted the identification of live birth with a sensitivity of 79.2% and a specificity of only 44.2%. In the prediction of a live birth following IVF, a distinction, however moderate, can be made between couples with a good and a poor prognosis. The success of IVF was found to mainly depend on maternal age and serum AMH concentrations, one of the most relevant and valuable markers of ovarian reserve.

METHODS: This study analyzed the database containing clinical and laboratory information on IVF treatment cycles carried out at the Mother–Infant Department of University Hospital, Modena between 2005 and 2008. The data was collected prospectively and recorded in the registered database in the fertility centre in Modena, Italy. Cycles were selected for analysis if all the following inclusion criteria were satisfied: (i) first IVF/ICSI attempt; (ii) a normal uterus and regular uterine cavity; (iii) no previous ovarian surgery; (iv) absence of severe male factor (defined as sperm count less than 1 x 10^6 ml or normal forms less than 5% according to World Health Organization (1999); (v) female age ≤42; (vi) absence of recurrent abortion; (vii) absence of antiphospholipid syndrome and any other relevant systemic condition; (viii) treatment with a long gonadotrophin-releasing hormone (GnRH) agonist protocol; (ix) complete computer-based patient records on anamnestic, clinical and IVF cycle characteristics and pregnancy follow-up; and (x) a stored serum sample taken within 3 months of commencing IVF suitable for measurement of AMH. All patients had been trying to conceive for at least 12 months and all had undergone a fertility workup.

RESULTS: A total of 389 patients were selected on the basis of inclusion criteria. Eight cycles were cancelled because of wrong drug administration, hence 381 patients constituted the population included in the statistical analysis. Of 381 started cycles, 15 were cancelled during ovarian stimulation because of excessive ovarian response and 13 because of absent or insufficient ovarian response. Of the 353 patients who had an oocyte retrieval, three had no oocytes retrieved and three had no fertilization; consequently, 347 patients had an embryo transfer procedure. Of the cohort, 101 of 381 women (26.5%) achieved a live birth.

CONCLUSIONS: The present study demonstrates that in the prediction of a live birth following IVF, a distinction, however moderate, can be made between couples with a good and a poor prognosis. The success of IVF was found to mainly depend on maternal age and serum AMH concentrations, one of the most relevant and valuable markers of ovarian reserve.
Anti-Müllerian hormone-tailored stimulation protocols improve outcomes whilst reducing adverse effects and costs of IVF.

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Abstract

BACKGROUND: Anti-Müllerian hormone (AMH) is increasingly used to quantify ovarian reserve, but it has not yet realized its full clinical potential in assisted reproduction technology. We investigated the possible benefits of using novel, stratified ovarian hyperstimulation protocols, tailored to individual AMH levels, compared with conventional stimulation.

METHODS: Retrospective data were collected from 769 women (first cycle of IVF, using fresh embryos), in a UK tertiary care unit: 346 women using conventional stimulation protocols; 423 women treated under new AMH-tailored protocols.

RESULTS: Embryo transfer rates increased significantly (79–87%; P = 0.002) after the introduction of AMH-tailored stimulation protocols. Pregnancy rate per cycle started and live birth rate also increased significantly compared with conventionally treated women (17.9–27.7%, P = 0.002 and 15.9–23.9%, P = 0.007, respectively). Moreover, in the AMH group, the incidence of the ovarian hyperstimulation syndrome (OHSS) fell significantly (6.9–2.3%, P = 0.002) and failed fertilization fell from 7.8 to 4.5%. The cost of fertility drug treatment fell by 29% per patient and the overall cost of clinical management of OHSS fell by 43% in the AMH group. GnRH antagonist protocols, introduced as part of AMH-tailored treatment, may have contributed to the observed improvements: however, within the AMH-tailored group, the live birth rate was not significantly different between agonist and antagonist-treated groups.

CONCLUSIONS: Although large, prospective, multicenter studies are indicated, we have clearly demonstrated that individualized, AMH-guided, controlled ovarian hyperstimulation protocols significantly improved positive clinical outcomes, reduced the incidence of complications and reduced the financial burden associated with assisted reproduction.
Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States.

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Abstract

OBJECTIVE: To determine age-specific serum anti-Müllerian hormone (AMH) values for women presenting to U.S. fertility clinics.

DESIGN: Retrospective study.

SETTING: Single clinical reference laboratory.

PATIENT(S): A total of 17,120 women of reproductive age ranging from 24 to 50 years old.

INTERVENTION(S): None.

MAIN OUTCOME MEASURE(S): Determination of single-year median and mean AMH values with SDs.

RESULTS: Single-year-specific median, mean, and SD values are summarized in Table 1. Both median and mean AMH values decreased steadily in a manner highly correlated with advancing age. The average yearly decrease in the median serum AMH value was 0.2 ng/mL/year through age 35 and then diminished to 0.1 ng/mL/year after age 35. The rate of decline in mean AMH values was 0.2 ng/mL/year through age 40 and then diminished to 0.1 ng/mL/year thereafter.

CONCLUSION(S): Median and mean AMH levels decreased steadily with increasing age from 24 to 50 years of age. Such data may be of value to physicians and their patients who are considering reproductive options.
Nomogram for the decline in serum anti-Müllerian hormone: a population study of 9,601 infertility patients.

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Abstract

OBJECTIVE: To define an optimal model for the decline in circulating anti-Müllerian hormone (AMH) with age and develop a validated age-related nomogram.

DESIGN: Cohort study with validation of linear, biphasic linear, differential, power, and quadratic equations undertaken in two additional cohorts.

SETTING: United Kingdom infertility clinics.

PATIENTS: Training cohort of 4,590 infertile women. Two separate validation cohorts; 4,588 infertile women, and 423 women with confirmed ovulation and normal pelvic ultrasound who have a male partner with severe oligospermia.

INTERVENTIONS: Serum AMH measurement.

MAIN OUTCOME MEASURES: Optimal fit and age-related AMH nomogram.

RESULTS: The linear model had the largest sum of absolute and squared residuals and provided a less adequate fit than the four nonlinear models. Of these, the R² ranged from 19.45% to 19.48% in the training dataset, from 21.30% to 21.36% in the validation dataset, and from 13.29% to 13.75% in the partners of oligospermic males. The parameters of the differential model were difficult to estimate, and the goodness-of-fit of the power model was slightly inferior to the quadratic model.

CONCLUSIONS: Circulating AMH concentrations decline with increasing reproductive age in a manner optimally described by a quadratic equation. This validated age-related AMH nomogram will enable counseling of infertility patients regarding reproductive performance.
Reference range for the anti-müllerian hormone Generation II assay: a population study of 10,984 women, with comparison to the established Diagnostics Systems Laboratory nomogram.

Abstract

OBJECTIVE: To develop an optimal model and age-specific centiles for the decline in antimüllerian hormone (AMH) as measured by the new Beckman Coulter AMH Generation II (Gen II) assay and compare this to the previous nomogram derived for the Diagnostics Systems Laboratory (DSL) assay.

DESIGN: Multicenter retrospective population study, with validation of linear, biphasic linear, differential, power, and quadratic equations.

SETTING: Two clinical pathology laboratories.

PATIENT(S): A new cohort of 10,984 women aged 25 to 45 years old attending infertility clinics, randomly divided into a training cohort of 5,492 women and a validation cohort of 5,492 women, and an existing cohort of 9,601 women, who had contributed to the development and validation of a nomogram for AMH measured by the DSL assay.

INTERVENTION(S): Serum measurement of AMH as determined by the Beckman Coulter AMH Generation II assay in 10,984 women.

MAIN OUTCOME MEASURE(S): Optimal model for the decline in AMH as measured by the AMH Gen II assay with age, with age-specific 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles.

RESULT(S): A quadratic model defined as \((2.431 + 0.089 \times \text{Age} + -0.003 \times \text{Age}^2)\) fitted the decline in AMH with age. The anticipated 40% increase in age-specific population values relative to the previously validated DSL assay nomogram was not observed.

CONCLUSION(S): Age-specific reference ranges for the AMH gen II assay suggest a systematic shift in assay calibration since initial evaluation and commercial release of the AMH Gen II assay.
A validated model of serum anti-müllerian hormone from conception to menopause.

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Abstract

BACKGROUND: Anti-Müllerian hormone (AMH) is a product of growing ovarian follicles. The concentration of AMH in blood may also reflect the non-growing follicle (NGF) population, i.e. the ovarian reserve, and be of value in predicting reproductive lifespan. A full description of AMH production up to the menopause has not been previously reported.

METHODOLOGY/PRINCIPAL FINDINGS: By searching the published literature for AMH concentrations in healthy pre-menopausal females, and using our own data (combined n = 3,260) we have generated and robustly validated the first model of AMH concentration from conception to menopause. This model shows that 34% of the variation in AMH is due to age alone. We have shown that AMH peaks at age 24.5 years, followed by a decline to the menopause. We have also shown that there is a neonatal peak and a potential pre-pubertal peak. Our model allows us to generate normative data at all ages.

CONCLUSIONS/SIGNIFICANCE: These data highlight key inflection points in ovarian follicle dynamics. This first validated model of circulating AMH in healthy females describes a transition period in early adulthood, after which AMH reflects the progressive loss of the NGF pool. The existence of a neonatal increase in gonadal activity is confirmed for females. An improved understanding of the relationship between circulating AMH and age will lead to more accurate assessment of ovarian reserve for the individual woman.
Human Reproduction, 2009 Apr;24(4):867-75.

Anti-Müllerian hormone-based approach to controlled ovarian stimulation for assisted conception.

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Abstract

BACKGROUND: Individualization of controlled ovarian stimulation (COS) for assisted conception is complicated by variable ovarian response to follicle stimulating hormone. We hypothesized that anti-Müllerian hormone (AMH), a predictor of oocyte yield, may facilitate treatment strategies for women undergoing COS, to optimize safety and clinical pregnancy rates.

METHODS: Prospective cohort study of 538 patients in two centres with differential COS strategies based on a centralized AMH measurement.

RESULTS: AMH was associated with oocyte yield after ovarian stimulation in both centres, and a ‘reduced’ AMH (1 to <5 pmol/l) was associated with a reduced clinical pregnancy rate. Women with a ‘normal’ AMH (5 to <15 pmol/l) treated with a long GnRH-agonist protocol (both centres) showed a low incidence of excess response (0%) and poor response (0%). In women with ‘high’ AMH (>15 pmol/l), the antagonist protocol eliminated the need for complete cryopreservation of embryos due to excess response (P <0.001) and showed a higher fresh cycle clinical pregnancy rate than agonist cycles [OR 4.40 (95% CI 1.95-9.93), P <0.001].

CONCLUSIONS: The use of circulating AMH to individualize treatment strategies for COS may result in reduced clinical risk, optimized treatment burden and maintained pregnancy rates, and is worthy of prospective randomized examination.
Can anti-Müllerian hormone concentrations be used to determine gonadotrophin dose and treatment protocol for ovarian stimulation?


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Abstract
The ability to predict the response potential of women to ovarian stimulation may allow the development of individualized ovarian stimulation protocols. This tailored approach to ovarian stimulation could reduce the incidence of ovarian hyperstimulation syndrome in women predicted to have an excessive response to stimulation or could improve pregnancy outcomes in women classed as poor responders. Namely, variation of the type of gonadotrophin-releasing hormone (GnRH) analogue or the form and dosage of gonadotrophin used for stimulation could be adjusted according to an individual’s response potential. The serum concentration of anti-Müllerian hormone (AMH) is established as a reliable marker of ovarian reserve, with decreasing concentrations correlated with reduced response potential. This review examines the current evidence evaluating individualized ovarian stimulation protocols using AMH concentration as a predictive marker of ovarian response. The rationale behind why specific treatment protocols based on individual response potential may be more suitable is also discussed. Based on current evidence, it appears that the use of AMH serum concentrations to predict ovarian response and optimize treatment strategies is a promising approach for improving pregnancy outcomes in women undergoing ovarian stimulation. However, prospective randomized controlled trials evaluating this approach are needed before any firm conclusions can be drawn.
Ovarian response markers lead to appropriate and effective use of corifollitropin alpha in assisted reproduction.

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Abstract
Corifollitropin alpha is a highly effective gonadotrophin, which maintains multifollicular growth for a week. The advantages of its administration include ease of use of the drug, making the treatment more patient friendly, resulting in a lower level of distress for the patient. At the same time, the pregnancy rate resulting from its use in IVF/intracytoplasmic sperm injection cycles is similar to that found when daily recombinant FSH is administered. The ovarian response to corifollitropin alpha is dependent on clinically established predictors such as baseline FSH, antral follicle count (AFC) and age. There is a general trend towards a higher ovarian response with an increasing AFC and the number of oocytes per attempt decreased with increasing baseline FSH and age. Even if the risk of ovarian hyperstimulation syndrome following corifollitropin alpha is very similar to the rate reported in literature for young women undergoing IVF, the risk of overstimulation may be reduced by avoiding maximal ovarian stimulation in women anticipated to be hyperresponders. High basal anti-Müllerian hormone and/or AFC can identify women with enhanced functional ovarian reserve at risk of overstimulation, and the risk is even higher if maximally stimulated with corifollitropin alpha or high dose of daily recombinant FSH. Corifollitropin alpha is a highly effective gonadotrophin which maintains multifollicular growth for a week. The ovarian response to corifollitropin was demonstrated to be dependent on clinically established predictors such as baseline FSH, antral follicle count (AFC) and age. There was a general trend toward a higher ovarian response with an increasing AFC and the mean number of oocytes per attempt decreased with increasing baseline FSH and age. Even if the risk of ovarian hyperstimulation syndrome (OHSS) following corifollitropin alpha is very similar to the rate of OHSS reported in literature for young women undergoing IVF, the risk of overstimulation may be reduced by avoiding maximal ovarian stimulation in women anticipated to be hyperresponders. Increasing evidence demonstrates that anti-Müllerian hormone and AFC exhibit a very good diagnostic performance in the prediction of hyperresponse. High basal anti-Müllerian hormone and/or AFC can identify women with enhanced functional ovarian reserve who are at risk of overstimulation if stimulated in IVF cycles and the risk is even higher if maximally stimulated with corifollitropin alpha or high dose of daily recombinant FSH.
Serum anti-Müllerian hormone predicts ovarian response and cycle outcome in IVF patients.

AUTHORS:  Wu CH, Chen YC, Wu HH, Yang JG, Chang YJ, Tsai HD.
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Abstract
PURPOSE: This prospective study was designed to investigate whether anti-Müllerian hormone (AMH) levels at basal and ovulation triggering day are associated with ovarian response and pregnancy outcome for in vitro fertilization (IVF).

METHOD: 60 infertility women undergoing IVF were prospectively studied. On day 3 of the menstrual cycle (D3), measurements of AMH, inhibin B, FSH, LH, and E2 and ultrasound evaluation of antral follicle count (AFC) were performed. Serum AMH and inhibin B levels were remeasured on the day of hCG administration (DhCG). The outcome measures were the number of retrieved oocytes and clinical pregnancy.

RESULTS: Number of retrieved oocytes was statistically significant and correlated with D3 AMH, AFC, DhCG AMH, DhCG inhibin B, FSH, and age (r = 0.885, 0.874, 0.742, 0.732, -0.521, -0.385, respectively). Statistically significant differences were found between pregnant and non-pregnant women regarding D3 AMH and AFC. Multiple regression analysis for prediction of pregnancy showed D3 AMH to be a good predictor of clinical pregnancy.

CONCLUSION: AMH correlates better than age, FSH, and inhibin B with the number of retrieved oocytes. Serum basal AMH may offer a better prognostic value for clinical pregnancy than other currently available markers of IVF outcome in our preliminary study.
Serum anti-Müllerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles—implications for individualization of therapy.

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Abstract
BACKGROUND: Serum concentrations of anti-Müllerian hormone (AMH) correlate with oocyte yield in assisted reproduction treatment (ART) cycles, however, performance of AMH for prediction of live birth is unknown.

METHODS: A total of 340 first cycle IVF/ICSI patients (median age 34.0 years, inter-quartile range 31.0-37.0 years), had basal plasma AMH and FSH measured and their predictive values for live birth and oocyte yield compared.

RESULTS: AMH predicts live birth [contribution to variance (CTV) 3.84%, P <0.001] and oocyte yield (r = 0.71, P < 0.0001, CTV 7.3%, P < 0.0001). Compared with age and FSH, AMH performs better in prediction of live births [area under receiver operating characteristic curve (AUC) 0.62, 95% CI 0.55-0.68; FSH AUC 0.42, 95% CI 0.35-0.49; age AUC 0.48, 95% CI 0.41-0.55, P = 0.0028] and excessive response to ovarian stimulation (AMH AUC 0.90, 95% CI 0.83-0.96; FSH AUC 0.32, 95% CI 0.23-0.40; age AUC 0.57, 95% CI 0.43-0.71, P < 0.001). AMH prediction of oocyte yield is independent of age (r = -0.28, P < 0.0001, CTV 1.4%, P = 0.006), however, a significant negative interaction (CTV 3.6%, P <0.0001) exists. AMH demonstrates improved differential distributions for non-, poor, normal and excessive ovarian responses relative to FSH and age.

CONCLUSIONS: Plasma AMH is a superior predictor of live birth and anticipated oocyte yield compared with FSH and age, facilitating individualization of therapy prior to first ART cycle.
Anti-Müllerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted reproductive technology.

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Abstract

BACKGROUND: Recently, a new marker, the anti-Müllerian hormone (AMH), has been evaluated as a marker of ovarian response. Serum AMH levels have been measured at frequent time-points during the menstrual cycle, suggesting the complete absence of fluctuation. The aim of this study was to evaluate whether serum AMH measurement on any day of the menstrual cycle could predict ovarian response in women undergoing assisted reproductive technology (ART).

METHODS: This study included 48 women attending the IVF/ICSI programme. Blood withdrawal for AMH measurement was performed in all the patients independently of the day of the menstrual cycle.

RESULTS: Women in the lowest AMH quartile (<0.4 ng/ml) were older and required a higher dose of recombinant FSH than women in the highest quartile (>7 ng/ml). All the cancelled cycles due to absent response were in the group of the lowest AMH quartile, whereas the cancelled cycles due to risk of ovarian hyperstimulation syndrome (OHSS) were in the group of the highest AMH quartile. This study demonstrated a strong correlation between serum AMH levels and ovarian response to gonadotrophin stimulation.

CONCLUSION: For the first time, clinicians may have a reliable serum marker of ovarian response that can be measured independently of the day of the menstrual cycle.
Circulating basal anti-Müllerian hormone levels as predictor of ovarian response in women undergoing ovarian stimulation for in vitro fertilization.

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Abstract

OBJECTIVE: To evaluate the clinical value of basal anti-Müllerian hormone (AMH) measurements compared with other available determinants, apart from chronologic age, in the prediction of ovarian response to gonadotrophin stimulation.

DESIGN: Prospective cohort study.

SETTING: Tertiary referral center for reproductive medicine and an IVF unit.

PATIENT(S): Women undergoing their first cycle of controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF).

MATERIALS AND METHODS: Basal levels of FSH and AMH as well as antral follicle count (AFC) were measured in 165 subjects. All patients were followed prospectively and their cycle outcomes recorded.

MAIN OUTCOME MEASURE(S): Predictive value of FSH, AMH, and AFC for extremes of ovarian response to stimulation.

RESULT(S): Out of the 165 women, 134 were defined as normal responders, 15 as poor responders, and 16 as high responders. Subjects in the poor response group were significantly older then those in the other two groups. Anti-Müllerian hormone levels and AFC were markedly raised in the high responders and decreased in the poor responders. Compared with FSH and AFC, AMH performed better in the prediction of excessive response to ovarian stimulation-AMH area under receiver operating characteristic curve (ROC(AUC)) 0.81, FSH ROC(AUC) 0.66, AFC ROC(AUC) 0.69. For poor response, AMH (ROC(AUC) 0.88) was a significantly better predictor than FSH (ROC(AUC) 0.83) but not AFC (ROC(AUC) 0.81). AMH prediction of ovarian response was independent of age and PCOS. Anti-Müllerian hormone cutoffs of >3.75 ng/mL and <1.0 ng/mL would have modest sensitivity and specificity in predicting the extremes of response.

CONCLUSION(S): Circulating AMH has the ability to predict excessive and poor response to stimulation with exogenous gonadotrophins. Overall, this biomarker is superior to basal FSH and AFC, and has the potential to be incorporated in to work-up protocols to predict patient’s ovarian response to treatment and to individualize strategies aiming at reducing the cancellation rate and the iatrogenic complications of COH.
Assessment of ovarian reserve with anti-Müllerian hormone: a comparison of the predictive value of anti-Müllerian hormone, follicle-stimulating hormone, inhibin B, and age.

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Abstract

OBJECTIVE: The objective of this study was to evaluate basal anti-Müllerian hormone as a marker for ovarian responsiveness to fertility treatment.

STUDY DESIGN: Frozen basal menstrual cycle day 3 serum samples were evaluated retrospectively for anti-Müllerian hormone, inhibin B, and follicle-stimulating hormone levels in 123 in vitro fertilization cycles (93 patients) and compared with in vitro fertilization records.

RESULTS: Anti-Müllerian hormone values correlated the best with the number of retrieved oocytes (r = 0.539; P < .001) relative to age (r = -0.323; P < .01), follicle-stimulating hormone (r = -0.317; P < .01), inhibin B (P > .05), luteinizing hormone (P > .05), and estradiol (r = -0.190; P < .05). Receiver operating characteristic curve analysis demonstrated that, for the prediction of <4 oocytes retrieved, antimüllerian hormone had the largest area under the curve (AUC = 0.81; P = .0001) relative to age (r = 0.74; P = .005), follicle-stimulating hormone (0.71; P = .02), inhibin B (0.66; P = .03), and estradiol (0.54; P > .05). Similarly, for the prediction of ≥15 retrieved oocytes, anti-Müllerian hormone had the largest area under the curve (0.80; P = .0001) relative to age (0.63; P = .02), follicle-stimulating hormone (0.64; P = .005), inhibin B (r = 0.57; P > .05), and estradiol (0.58; P > .05).

CONCLUSION: Anti-Müllerian hormone correlates better than age, follicle-stimulating hormone, luteinizing hormone, inhibin B, and estradiol with the number of retrieved oocytes. Receiver operating characteristic curves estimated that anti-Müllerian hormone accurately predicts ovarian responsiveness to controlled ovarian stimulation with high sensitivity and specificity.
Anti-Müllerian hormone testing is useful for individualization of stimulation protocols in oocyte donors.


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Abstract

While the age of a donor is a fundamental factor to the success of donor IVF, no serum markers have been demonstrated to be useful in predicting variability of ovarian response in individual donors. Anti-Müllerian hormone (AMH) has been described as an accurate marker of ovarian response in patients undergoing IVF, but has not been applied to oocyte donors. AMH concentrations from 104 anonymous oocyte donors between the ages of 21-32 years were studied and IVF outcome parameters compared. AMH was correlated with several parameters including the number of oocytes retrieved ($r = 0.232$, $P = 0.024$), the peak oestradiol concentrations ($r = 0.235$, $P = 0.024$) and the need to decrease gonadotrophin dose in order to avoid ovarian hyperstimulation syndrome ($r = 0.274$, $P = 0.007$). Receiver operating curve analysis was able to identify an AMH threshold that rendered about 70% sensitivity and 70% specificity for predicting the need to decrease gonadotrophin dosing. The clinical pregnancy rate was 77% per recipient and was not related to the donors’ AMH concentrations. For oocyte donors, measurement of AMH appears most useful for determining gonadotrophin sensitivity in order to mitigate symptoms consistent with ovarian hyperstimulation.
Comparison of inter- and intra-cycle variability of anti-Müllerian hormone and antral follicle counts.

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Abstract
BACKGROUND: The antral follicle count (AFC) and anti-Müllerian hormone (AMH) both represent age-related follicular decline quite accurately, although long-term follow-up studies are still lacking. The best ovarian reserve test would need only a single, cycle-independent measurement to be representative.

METHODS: To compare the inter- and intra-cycle stability of AFC and AMH, we used age-adjusted intra-class correlation coefficients (ICCs). To measure inter-cycle stability across a number of up to four menstrual cycles, we used data, prospectively collected for the purpose of another study, from 77 regularly cycling, infertile women aged 24-40 years. AMH and AFC values were measured on cycle day 3. To study intra-cycle variability, we used data from a prospective cohort study of 44 regularly cycling volunteers, aged 25-46 years and measured AMH and assessed the AFC (2-10 mm) every 1-3 cycle days.

RESULTS: Between menstrual cycles, AFC and AMH varied between 0 and 25 follicles (median 10), and 0.3 and 27.1 ng/ml (median 4.64). The difference in age-adjusted ICC between AMH [ICC, 0.89 (95% CI, 0.84-0.94)] and AFC [ICC, 0.71 (95% CI, 0.63-0.77)] was 0.18 (95% CI, 0.12-0.27). For the intra-cycle variation, 0-43 antral follicles (median 7) were counted per volunteer. The difference in age-adjusted ICC between AMH [ICC, 0.87 (95% CI, 0.82-0.91)] and AFC [ICC, 0.69 (95% CI, 0.46-0.82)] was 0.18 (95% CI, 0.034-0.42).

CONCLUSIONS: Serum AMH demonstrated less individual intra- and inter-cycle variation than AFCs and may therefore be considered a more reliable and robust means of assessing ovarian reserve in subfertile women.
How Much Does AMH Really Vary in Normal Women?

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Abstract

Anti-Mullerian Hormone (AMH) is an ovarian hormone expressed in growing follicles that have undergone recruitment from the primordial follicle pool but have not yet been selected for dominance. It is considered an accurate marker of ovarian reserve, able to reflect the size of the ovarian follicular pool of a woman of reproductive age. In comparison to other hormonal biomarkers such as serum FSH, low intra- and intermenstrual cycle variability have been proposed for AMH. This review summarizes the knowledge regarding within-subject variability, with particular attention on AMH intracycle variability. Moreover the impact of ethnicity, body mass index, and smoking behaviour on AMH interindividual variability will be reviewed. Finally changes in AMH serum levels in two conditions of ovarian quiescence, namely contraceptives use and pregnancy, will be discussed. The present review aims at guiding researchers and clinicians in interpreting AMH values and fluctuations in various research and clinical scenarios.
Anti-Müllerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART).

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Abstract

BACKGROUND: In women, anti-Müllerian hormone (AMH) levels may represent the ovarian follicular pool and could be a useful marker of ovarian reserve. The clinical application of AMH measurement has been proposed in the prediction of quantitative and qualitative aspects in assisted reproductive technologies (ART). In men, AMH is secreted in both the serum and seminal fluid. Its measurement may be useful in clinical evaluation of the infertile male.

METHODS: The PubMed database was systematically searched for studies published until the end of January 2009, search criteria relevant to AMH, ovarian reserve, ovarian response to gonadotrophin stimulation, spermatogenesis and azoospermia were used.

RESULTS: AMH seems to be a better marker in predicting ovarian response to controlled ovarian stimulation than age of the patient, FSH, estradiol and inhibin B. A similar performance for AMH and antral follicular count has been reported. In clinical practice, AMH measurement may be useful in the prediction of poor response and cycle cancellation and also of hyper-response and ovarian hyperstimulation syndrome. In the male, the wide overlap of AMH values between controls and infertile men precludes this hormone from being a useful marker of spermatogenesis.

CONCLUSIONS: As AMH may permit the identification of both the extremes of ovarian stimulation, a possible role for its measurement may be in the individualization of treatment strategies in order to reduce the clinical risk of ART along with optimized treatment burden. It is fundamental to clarify the cost/benefit of its use in ovarian reserve testing.
Prediction of an excessive response in in vitro fertilization from patient characteristics and ovarian reserve tests and comparison in subgroups: an individual patient data meta-analysis.


CENTER: 1Department of Reproductive Medicine and Gynaecology, University Medical Center Utrecht, Utrecht, the Netherlands.

Abstract

OBJECTIVE: To evaluate whether ovarian reserve tests (ORTs) add prognostic value to patient characteristics, such as female age, in the prediction of excessive response to ovarian hyperstimulation in patients undergoing IVF, and whether their performance differs across clinical subgroups.

DESIGN: Authors of studies reporting on basal FSH, antimüllerian hormone (AMH), or antral follicle count (AFC) in relation to ovarian response to ovarian hyperstimulation were invited to share original data. Random intercept logistic regression models were used to estimate added value of ORTs on patient characteristics, while accounting for between-study heterogeneity. Receiver operating characteristic regression analyses were performed to study the effect of patient characteristics on ORT accuracy.

SETTING: In vitro fertilization clinics.

PATIENT(S): A total of 4,786 women for the main analysis, with a subgroup of 1,023 women with information on all three ORTs.

INTERVENTION(S): None.

MAIN OUTCOME MEASURE(S): Excessive response prediction.

RESULT(S): We included 57 studies reporting on 32 databases. Female age had an area under the receiver operating characteristic curve of 0.61 for excessive response prediction. Antral follicle count and AMH significantly added prognostic value to this. A model with female age, AFC, and AMH had an area under the receiver operating characteristic curve of 0.85. The combination of AMH and AFC, without age, had similar accuracy. Subgroup analysis indicated that FSH performed significantly worse in predicting excessive response in higher age groups, AFC did significantly better, and AMH performed the same.

CONCLUSION(S): We demonstrate that AFC and AMH add value to female age in the prediction of excessive response and that, for AFC and FSH, the discriminatory performance is affected by female age.
Hum Reprod Update, 2014 May 12.

Anti-Mullerian hormone: ovarian reserve testing and its potential clinical implications.

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Abstract

BACKGROUND: In women, anti-Müllerian hormone (AMH) is exclusively produced by granulosa cells of ovarian follicles during the early stages of follicle development. After an initial increase until early adulthood, AMH concentrations slowly decrease with increasing age until becoming undetectable ∼5 years before menopause when the stock of primordial follicles is exhausted. However, major individual variability exists in the pace of follicle pool depletion and the initial size of the follicle pool, reflected by a wide range of age at menopause. Individual AMH serum concentration does accurately reflect the size of the pool of antral follicles, representing the quantity of the remaining primordial follicles. Accordingly, AMH levels may vary significantly in women of the same chronological age, allowing AMH to predict the remaining length of a woman’s reproductive lifespan.

METHODS: Following 10 years of intense clinical research in this area (with over 300 papers published in core clinical journals every year), the level of evidence justifying use of AMH in ovarian reserve testing is rapidly increasing. We have conducted a summarizing review regarding all evidence published.

RESULTS: Many studies have convincingly demonstrated that AMH is the best currently available measure of ovarian reserve under a variety of clinical situations, such as infertility treatment (especially IVF), the forecasting of reproductive lifespan, ovarian dysfunction (especially polycystic ovary syndrome) and gonadotoxic cancer treatment or ovarian surgery. Moreover, AMH may help to individualize dosing for ovarian stimulation thereby improving the efficiency and safety of IVF. However, there are concerns about the performance of the AMH assay under different conditions regarding storage of samples and handling techniques. Therefore an international guideline for laboratories and a reference preparation are needed to make test results between laboratories truly comparable.

CONCLUSIONS: AMH is the best current available measure of ovarian reserve for different clinical conditions. However, prospective well powered studies comparing different infertility treatment strategies based on initial AMH levels using appropriate end-points, such as live birth and cost-effectiveness, are urgently awaited. Such studies could represent a true step forward in rendering counseling and infertility care more patient tailored.
The predictive accuracy of anti-Müllerian hormone for live birth after assisted conception: a systematic review and meta-analysis of the literature.

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\(^5\) Reproductive and Maternal Medicine, School of Medicine, University of Glasgow, G12 8QQ Glasgow, UK.

Abstract

BACKGROUND: Anti-Müllerian hormone (AMH) is an established marker of ovarian reserve and a good predictor of poor or excessive ovarian response after controlled hyperstimulation. However, it is unclear whether it can predict the ultimate outcome of assisted conception, live birth. We undertook a systematic review and meta-analysis to examine whether AMH is a predictor of live birth in women undergoing assisted conception.

METHODS: The study was conducted according to the PRISMA guidelines. PubMed, Embase, Medline, Web of Knowledge and the Cochrane trial register and unpublished literature were searched. Studies fulfilling the eligibility criteria were included in the systematic review and those with extractable data were included in the meta-analysis. Quality assessment was performed with the QUADAS 2 checklist. A summary estimate of diagnostic odds ratio (DOR) was derived using the random effects model for binary data. A hierarchical summary receiver operating characteristic model provided pooled estimates before and after adjusting for age and AMH assay as covariates.

RESULTS: Out of 361 non-duplicate studies, 47 were selected; 17 met the eligibility criteria and 13 had extractable data and thus were included in the meta-analysis. Three out of the 13 studies included only women with expected low ovarian reserve and were analysed individually from the remaining 10 to minimize heterogeneity. The DOR for women with unknown ovarian reserve (n = 5764 women) was 2.39 (95% confidence interval (CI): 1.85-3.08). After adjustment for age the DOR was little changed at 2.48 (95% CI: 1.81-3.22) and the DOR adjusted for AMH assay was almost identical at 2.42 (95% CI: 1.86-3.14). For women with expected low ovarian reserve (n = 542 women) the DOR was 4.63 (95% CI: 2.75-7.81).

CONCLUSIONS: AMH, independently of age, has some association with predicting live birth after assisted conception and may be helpful when counselling couples before undergoing fertility treatment. However, its predictive accuracy is poor.
Reproductive and lifestyle determinants of anti-Müllerian hormone in a large population-based study.

AUTHORS: Dólleman M¹, Verschuren WM, Eijkemans MJ, Dollé ME, Jansen EH, Broekmans FJ, van der Schouw YT.

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Abstract

CONTEXT: Anti-müllerian hormone (AMH) is an ovarian reserve marker that is increasingly applied in clinical practice as a prognostic and diagnostic tool. Despite increased use of AMH in clinical practice, large-scale studies addressing the influence of possible determinants on AMH levels are scarce.

OBJECTIVE: We aimed to address the role of reproductive and lifestyle determinants of AMH in a large population-based cohort of women.

DESIGN: In this cross-sectional study, age-specific AMH percentiles were calculated using general linear modeling with CG-LMS (Cole and Green, Lambda, Mu, and Sigma model, an established method to calculate growth curves for children).

SETTING: Women from the general community participating in the Doetinchem Cohort study were assessed.

PARTICIPANTS: Two thousand three hundred twenty premenopausal women were included.

MAIN OUTCOME MEASURE: The effect of female reproductive and lifestyle factors on shifts in age-specific AMH percentiles was studied.

RESULTS: In comparison to women with a regular menstrual cycle, current oral contraceptive (OC) users, women with menstrual cycle irregularity, and pregnant women had significantly lower age-specific AMH percentiles (for OC use, 11 percentiles lower; for cycle irregularity, 11 percentiles lower; and for pregnancy, 17 percentiles lower [P value for all < 0.0001]). Age at menarche and age at first childbirth were not associated with the age-specific AMH percentile. Higher parity was associated with 2 percentiles higher age-specific AMH (P = 0.02). Of the lifestyle factors investigated, current smoking was associated with 4 percentiles lower age-specific AMH percentiles (P = 0.02), irrespective of the smoking dose. Body mass index, waist circumference, alcohol consumption, physical exercise, and socioeconomic status were not significantly associated with age-specific AMH percentiles.

CONCLUSIONS: This study demonstrates that several reproductive and lifestyle factors are associated with age-specific AMH levels. The lower AMH levels associated with OC use and smoking seem reversible, as effects were confined to current use of OC or cigarettes. It is important to give careful consideration to the effect of such determinants when interpreting AMH in a clinical setting and basing patient management on AMH.
Anti-Müllerian hormone, the assessment of the ovarian reserve, and the reproductive outcome of the young patient with cancer.

AUTHORS: Anderson RA, Wallace WH.
CENTER: Medical Research Council Centre for Reproductive Health, University of Edinburgh, Edinburgh, United Kingdom.

Abstract
The accurate assessment of the ovarian reserve has long been a key goal in reproductive medicine. The recognition that serum antimüllerian hormone provides an indirect measure of the ovarian reserve has led to its rapid adoption in assisted conception, and wide exploration of its potential across the reproductive lifespan from the neonate to the menopause. In this short review we discuss its relationship with the ovarian reserve in its varied meanings, and in various contexts. These include in childhood and adolescence, and in the assessment of the impact of cancer therapy on the female reproductive tract. These therapies can adversely impact all aspects of female reproduction, including hypothalamic, pituitary, and ovarian hormonal activity, and the ability of the uterus to support a successful pregnancy.
Why we may abandon basal follicle-stimulating hormone testing: a sea change in determining ovarian reserve using anti-Müllerian hormone.

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Abstract
Anti-müllerian hormone is the most informative serum marker of ovarian reserve currently available and should be considered an important part of any contemporary reproductive medicine practice. It is both more convenient and informative than basal FSH and can be assessed at any point in the cycle. It is the most useful serum method of determining ovarian reserve, which guides pretreatment counseling, choice of infertility treatment, and avoidance of ovarian hyperstimulation. The future role of basal FSH testing is in doubt.
Anti-Müllerian hormone levels are strongly associated with live-birth rates after assisted reproduction.

AUTHORS: Brodin T, Hadziosmanovic N, Berglund L, Olovsson M, Holte J.
CENTER: 1 Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden.

Abstract

CONTEXT: Previous studies have suggested that antimüllerian hormone (AMH) levels are positively associated with in vitro fertilization (IVF) outcome through their relationship with oocyte yield and not by reflecting oocyte or embryo quality.

OBJECTIVE: The aim was to investigate whether AMH levels are associated with pregnancy and live-birth rates and whether the results may also reflect qualitative aspects of oocytes and embryos.

DESIGN: The study was a prospective cohort study between April 2008 and June 2011.

SETTING: The study was done at a university-affiliated private infertility center.

PATIENTS: The study cohort consisted of 892 consecutive women undergoing 1230 IVF-intracytoplasmic sperm injection cycles.

INTERVENTION(S): AMH levels, analyzed using the DSL ELISA kit, were statistically adjusted for repeated treatments and age and analyzed for associations with treatment outcome.

MAIN OUTCOME MEASURES: Pregnancy rates, live-birth rates, and stimulation outcome parameters were measured.

RESULTS: AMH was log-normally distributed with a mean (SD) of 2.3 (2.5) ng/mL. Live-birth rates per started cycle (mean [95% confidence interval]) increased log-linearly from 10.7% [7.2-14.1] for AMH < 0.84 ng/mL (25th percentile) to 30.8% [25.7-36.0] for AMH > 2.94 ng/mL (75th percentile), Ptrend < .0001, being superior in women with polycystic ovaries. These findings were significant also after adjustments were made for age and oocyte yield. AMH was also associated with ovarian response variables and embryo scores.

CONCLUSIONS: AMH is strongly associated with live-birth rates after IVF-intracytoplasmic sperm injection. AMH may therefore serve as a prognostic factor for the chance of a pregnancy and live birth. Treatment outcome was superior in patients with polycystic ovaries. The findings also indicate that AMH may partially comprise information about oocyte quality.
Anti-Müllerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients.

AUTHORS: Arce JC¹, La Marca A, Mirner Klein B, Nyboe Andersen A, Fleming R.

CENTER: ¹Reproductive Health, Ferring Pharmaceuticals A/S, Copenhagen, Denmark.

Abstract

OBJECTIVE: To assess the relationships between serum antimüllerian hormone (AMH) and ovarian response and treatment outcomes in good-prognosis patients undergoing controlled ovarian stimulation using a gonadotropin-releasing hormone (GnRH) antagonist protocol.

DESIGN: Secondary analysis of data prospectively collected in a randomized, assessor-blind trial comparing two different gonadotropin preparations with respect to ongoing pregnancy rate.

SETTING: Twenty-five centers in seven countries.

PATIENT(S): 749 women, aged 21 to 34 years, with primary diagnosis of infertility being unexplained infertility or mild male factor infertility and with serum follicle-stimulating hormone (FSH) level 1-12 IU/L and antral follicle count (AFC) ≥10.

INTERVENTION(S): Controlled ovarian stimulation with highly purified human menopausal gonadotropin (hPHMG) or recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer and potential subsequent 1-year cryopreserved blastocyst replacement in natural cycles.

MAIN OUTCOME MEASURE(S): Relationships between AMH at start of stimulation and ovarian response and treatment outcome.

RESULT(S): Serum AMH concentration was strongly correlated with oocyte yield: AMH accounted for 85%, FSH for 14%, and inhibin B and AFC for <1% of the explained variation in oocyte yield. Also, AMH showed a high accuracy for the prediction of poor (≤3 oocytes) and high response (≥15 oocytes), which was statistically significantly better than basal FSH, AFC, or inhibin B. AMH was statistically significantly positively associated with ongoing pregnancy rate in the fresh cycle as well as with the 1-year cumulative ongoing pregnancy and live-birth rates.

CONCLUSION(S): There is a positive relationship between AMH and oocyte yield in GnRH antagonist cycles, and AMH is the best predictor for identifying patients with poor and high ovarian response. The positive association between AMH and cumulative live-birth rates after fresh and cryopreserved cycles reflects the availability of more oocytes/blastocysts, not higher quality.
Anti-Mullerian hormone as a predictor of follicular reserve in ovarian insufficiency: special emphasis on FSH-resistant ovaries.

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Abstract

BACKGROUND: Anti-Müllerian hormone (AMH) is secreted by ovarian granulosa cells and its serum levels reflect ovarian follicle reserve. The main objective of this study was to test the use of AMH assay in identifying women with primary amenorrhea (PA) and existing follicles and to study follicle phase dependent AMH secretion.

METHODS: Serum levels of AMH were measured in subjects with FSH-resistant ovaries (FSHRO, n=12), primary ovarian insufficiency (POI) with PA (n=11) or secondary amenorrhea (SA n=20) of unknown etiology, and controls (n=23), and in Turner syndrome (TS) [45,X (n=18), mosaicism (n=7), structural X chromosome abnormalities (SCA, n=10)], and healthy controls (n=34).

RESULTS: Serum levels of AMH in women with FSHRO were comparable with those in control women (2.76 ± 2.37 versus 3.77 ± 2.36 ng/ml) and significantly higher than in women with PA (0.05 ± 0.04 ng/ml; P < 0.001) or SA of unknown origin (0.12 ± 0.20 ng/ml; P < 0.001). TS girls/women with 45,X or SCA had low serum AMH levels (0.13 ± 0.09 and 0.27 ± 0.19 ng/ml) compared with their controls (3.34 ± 2.23 ng/ml) or subjects with mosaicism (2.33 ± 2.81 ng/ml). AMH expression was detected in granulosa cells of women with FSHRO but not in any of the 45,X fetal ovarian specimens.

CONCLUSIONS: A serum AMH assay could be used to identify patients with decreasing ovarian reserves and POI. Moreover, our results support the notion that AMH is secreted mainly by small non-selected follicles, since follicular granulosa cells were AMH-positive and serum AMH levels were normal/low normal in women with FSHRO, who lack follicle development beyond the small antral stage.
Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice.

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Center: Mother-Infant Department, Institute of Obstetrics and Gynaecology, University of Modena and Reggio Emilia, 41100 Modena, Italy.

Abstract

Background: The main objective of individualization of treatment in IVF is to offer every single woman the best treatment tailored to her own unique characteristics, thus maximizing the chances of pregnancy and eliminating the iatrogenic and avoidable risks resulting from ovarian stimulation. Personalization of treatment in IVF should be based on the prediction of ovarian response for every individual. The starting point is to identify if a woman is likely to have a normal, poor or a hyper response and choose the ideal treatment protocol tailored to this prediction. The objective of this review is to summarize the predictive ability of ovarian reserve markers, such as antral follicle count (AFC) and anti-Müllerian hormone (AMH), and the therapeutic strategies that have been proposed in IVF after this prediction.

Methods: A systematic review of the existing literature was performed by searching Medline, EMBASE, Cochrane library and Web of Science for publications in the English language related to AFC, AMH and their incorporation into controlled ovarian stimulation (COS) protocols in IVF. Literature available to May 2013 was included.

Results: The search generated 305 citations of which 41 and 25 studies, respectively, reporting the ability of AMH and AFC to predict response to COS were included in this review. The literature review demonstrated that AFC and AMH, the most sensitive markers of ovarian reserve identified to date, are ideal in planning personalized COS protocols. These sensitive markers permit prediction of the whole spectrum of ovarian response with reliable accuracy and clinicians may use either of the two markers as they can be considered interchangeable. Following the categorization of expected ovarian response to stimulation clinicians can adopt tailored therapeutic strategies for each patient. Current scientific trend suggests the elective use of the GnRH antagonist based regimen for hyper-responders, and probably also poor responders, as likely to be beneficial. The selection of the appropriate and individualized gonadotrophin dose is also of paramount importance for effective COS and subsequent IVF outcomes.

Conclusion: Personalized IVF offers several benefits; it enables clinicians to give women more accurate information on their prognosis thus facilitating counselling especially in cases of extremes of ovarian response. The deployment of therapeutic strategies based on selective use of GnRH analogues and the fine tuning of the gonadotrophin dose on the basis of potential ovarian response in every single woman can allow for a safer and more effective IVF practice.
Measuring anti-Müllerian hormone for the assessment of ovarian reserve: when and for whom is it indicated?

AUTHORS: Anderson RA, Nelson SM, Wallace WH.

CENTER: Division of Reproductive and Developmental Sciences, University of Edinburgh, Edinburgh, Scotland, UK.

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.
ESHRE consensus on the definition of ‘poor response’ to ovarian stimulation for in vitro fertilization: the Bologna criteria.

AUTHORS: Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L; ESHRE working group on Poor Ovarian Response Definition.

CENTER: S.I.S.Me.R Reproductive Medicine Unit, Via Mazzini 12, 40138 Bologna, Italy.

Abstract

The definition presented here represents the first realistic attempt by the scientific community to standardize the definition of poor ovarian response (POR) in a simple and reproducible manner. POR to ovarian stimulation usually indicates a reduction in follicular response, resulting in a reduced number of retrieved oocytes. It has been recognized that, in order to define the poor response in IVF, at least two of the following three features must be present: (i) advanced maternal age or any other risk factor for POR; (ii) a previous POR; and (iii) an abnormal ovarian reserve test (ORT). Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT. By definition, the term POR refers to the ovarian response, and therefore, one stimulated cycle is considered essential for the diagnosis of POR. However, patients of advanced age with an abnormal ORT may indicate reduced ovarian reserve and act as a surrogate of ovarian stimulation cycle outcome. In this case, the patients should be more properly defined as ‘expected poor responder’. If this definition of POR is uniformly adapted as the ‘minimal’ criteria needed to select patients for future clinical trials, more homogeneous populations will be tested for any new protocols. Finally, by reducing bias caused by spurious POR definitions, it will be possible to compare results and to draw reliable conclusions.
REPRODUCTIVE LIFECYCLE

“Women over 30 who have not completed their family and still plan to defer pregnancy should seriously consider having their AMH levels checked.”

Prof. William Ledger, MA, DPhil (Oxon), MB, ChB, FRCOG, FRANZCOG
Head & Professor of Obstetrics and Gynaecology
School of Women’s & Children’s Health
University of New South Wales
Sydney, Australia
Changes in anti-Müllerian hormone (AMH) throughout the life span: a population-based study of 1,027 healthy males from birth (cord blood) to the age of 69 years.

AUTHORS:  Aksglaede L¹, Sørensen K¹, Boas M¹, Mouritsen A¹, Hagen CP¹, Jensen RB¹, Petersen JH¹,², Linneberg A³, Andersson AM¹, Main KM¹, Skakkebæk NE¹, Juul A¹.

CENTER: ¹University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark ²Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark ³Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark

Abstract

CONTEXT: Anti-Müllerian hormone (AMH), which is secreted by immature Sertoli cells, triggers the involution of the fetal Müllerian ducts. AMH is a testis-specific marker used for diagnosis in infants with ambiguous genitalia or bilateral cryptorchidism.

AIM: The aim of the study was to describe the ontogeny of AMH secretion through life in healthy males.

SETTING: This was a population-based study of healthy volunteers.

PARTICIPANTS: Participants included 1027 healthy males from birth (cord blood) to 69 years. A subgroup was followed up longitudinally through the infantile mini-puberty [(in cord blood, and at 3 and 12 months), n = 55] and another group through puberty [(biannual measurements), n = 83].

MAIN OUTCOME MEASURES: Serum AMH was determined by a sensitive immunoassay. Serum testosterone, LH, and FSH were measured, and pubertal staging was performed in boys aged 6-20 years (n = 616).

RESULTS: Serum AMH was above the detection limit in all samples with a marked variation according to age and pubertal status. The median AMH level in cord blood was 148 pmol/liter and increased significantly to the highest observed levels at 3 months (P < 0.0001). AMH declined at 12 months (P < 0.0001) and remained at a relatively stable level throughout childhood until puberty, when AMH declined progressively with adults exhibiting 3–4% of infant levels.

CONCLUSIONS: Based on this extensive data set, we found detectable AMH serum levels at all ages, with the highest measured levels during infancy. At the time of puberty, AMH concentrations declined and remained relatively stable throughout adulthood. The potential physiological role of AMH and clinical applicability of AMH measurements remain to be determined.
Serum levels of anti-Müllerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients.


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2 Department of Pediatrics, Hillerød Hospital, Hillerød, Denmark
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Abstract

BACKGROUND: In adult women, anti-Müllerian hormone (AMH) is related to the ovarian follicle pool. Little is known about AMH in girls.

OBJECTIVE: The objective of the study was to provide a reference range for AMH in girls and adolescents and to evaluate AMH as a marker of ovarian function.

SETTING: The study was conducted at a tertiary referral center for pediatric endocrinology.

MAIN OUTCOME MEASURES: We measured AMH in 926 healthy females (longitudinal values during infancy) as well as in 172 Turner syndrome (TS) patients according to age, karyotype (A: 45,X; B: miscellaneous karyotypes; C: 45,X/46,XX), and ovarian function (1: absent puberty; 2: cessation of ovarian function; 3: ongoing ovarian function).

RESULTS: AMH was undetectable in 54% (38 of 71) of cord blood samples (<2; <2–15 pmol/liter) (median; 2.5th to 97.5th percentile) and increased in all (37 of 37) infants from birth to 3 months (15; 4.5–29.5 pmol/liter). From 8-25 years, AMH levels were stable (19.9; 4.7–60.1 pmol/liter), with the lower level of the reference range clearly above the detection limit. AMH levels were associated with TS-karyotype groups (median A vs B: <2 vs 3 pmol/liter, P = 0.044; B vs C: 3 vs 16 pmol/liter, P <0.001) as well as with ovarian function (absent puberty vs cessation of ovarian function: <2 vs 6 pmol/liter, P = 0.004; cessation of ovarian function vs ongoing ovarian function: 6 vs 14 pmol/liter, P = 0.001). As a screening test of premature ovarian failure in TS, the sensitivity and specificity of AMH less than 8 pmol/liter was 96 and 86%, respectively.

CONCLUSION: AMH seems to be a promising marker of ovarian function in healthy girls and TS patients.
Relationship of serum anti-Müllerian hormone concentration to age at menopause.

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Abstract
BACKGROUND: Serum anti-Müllerian hormone (AMH) levels are highly correlated with antral follicle counts, while being menstrual cycle independent and easily measurable. However, AMH, unlike antral follicle counts, has not been tested as yet as a predictor of reproductive status. By relating AMH levels to the age distribution of reproductive events like onset of menopause, we tested this hypothesis.

METHODS: AMH levels were measured in 144 fertile normal volunteers and used to determine an estimate of mean AMH as a function of age. Data on the onset of menopause were obtained from the population-based Prospect-European Prospective Investigation into Cancer and Nutrition (Prospect-EPIC) cohort. Estimation of an AMH threshold to predict menopause was done by maximum likelihood using the observed (Prospect-EPIC) distribution of age at menopause and the predictive distribution from this AMH threshold. Predictions of age at menopause follow from an individual woman’s AMH relative to percentiles of the distribution of AMH for a given age, and the corresponding percentiles of the predictive distribution of age at menopause.

RESULTS: There was good conformity between the observed distribution of age at menopause and that predicted from declining AMH levels.

CONCLUSIONS: The similarity between observed and predictive distributions of age at menopause supports the hypothesis that AMH levels are related to onset of menopause. Results of this study suggest that AMH is able to specify a woman’s reproductive age more realistically than chronological age alone.
Anti-mullerian hormone as a predictor of time to menopause in late reproductive age women.

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Abstract

CONTEXT: Anti-mullerian hormone (AMH) has emerged as a marker of ovarian reserve and a possible surrogate measure of reproductive aging.

OBJECTIVE: The aim of the study was to evaluate the predictive value of AMH levels in determining the median time to menopause for late reproductive age women and the predictive ability of AMH compared to FSH and inhibin b.

DESIGN AND SETTING: A 14-yr follow-up in the Penn Ovarian Aging Study, 1996-2010, was conducted for a randomly identified population-based cohort.

SUBJECTS: A total of 401 late reproductive age women participated in the study.

MAIN OUTCOME MEASURE: Observed time to menopause was measured.

RESULTS: All participants were premenopausal, with a mean (SD) age of 41.47 (3.52) yr and a median AMH level of 0.68 ng/ml at baseline. AMH strongly predicted time to menopause; age further improved predictions. Among women with a baseline AMH level below 0.20 ng/ml, the median time to menopause was 5.99 yr [95% confidence interval (CI), 4.20-6.33] in the 45- to 48-yr age group and 9.94 yr (95% CI, 3.31-12.73) in the 35- to 39-yr age group. With higher baseline AMH levels above 1.50 ng/ml, the median time to menopause was 6.23 yr in the oldest age group and more than 13.01 yr in the youngest age group. Smoking significantly reduced the time to menopause (hazard ratio, 1.61; 95% CI, 1.19-2.19; P = 0.002). AMH was a stronger predictor of time to menopause than FSH or inhibin b.

CONCLUSIONS: AMH is a strong predictor of median time to menopause in late reproductive age women. Age and smoking are significant and independent contributors to the predictions of AMH.
The relationship between anti-Müllerian hormone in women receiving fertility assessments and age at menopause in subfertile women: evidence from large population studies.


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Abstract

CONTEXT: Anti-Müllerian hormone (AMH) concentration reflects ovarian aging and is argued to be a useful predictor of age at menopause (AMP). It is hypothesized that AMH falling below a critical threshold corresponds to follicle depletion, which results in menopause. With this threshold, theoretical predictions of AMP can be made. Comparisons of such predictions with observed AMP from population studies support the role for AMH as a forecaster of menopause.

OBJECTIVE: The objective of the study was to investigate whether previous relationships between AMH and AMP are valid using a much larger data set.

SETTING: AMH was measured in 27,563 women attending fertility clinics.

STUDY DESIGN: From these data a model of age-related AMH change was constructed using a robust regression analysis. Data on AMP from subfertile women were obtained from the population-based Prospect-European Prospective Investigation into Cancer and Nutrition (Prospect-EPIC) cohort (n = 2249). By constructing a probability distribution of age at which AMH falls below a critical threshold and fitting this to Prospect-EPIC menopausal age data using maximum likelihood, such a threshold was estimated.

MAIN OUTCOME: The main outcome was conformity between observed and predicted AMP.

RESULTS: To get a distribution of AMH-predicted AMP that fit the Prospect-EPIC data, we found the critical AMH threshold should vary among women in such a way that women with low age-specific AMH would have lower thresholds, whereas women with high age-specific AMH would have higher thresholds (mean 0.075 ng/mL; interquartile range 0.038–0.15 ng/mL). Such a varying AMH threshold for menopause is a novel and biologically plausible finding. AMH became undetectable (<0.2 ng/mL) approximately 5 years before the occurrence of menopause, in line with a previous report.

CONCLUSIONS: The conformity of the observed and predicted distributions of AMP supports the hypothesis that declining population averages of AMH are associated with menopause, making AMH an excellent candidate biomarker for AMP prediction. Further research will help establish the accuracy of AMH levels to predict AMP within individuals.

Anti-Müllerian hormone predicts menopause: a long-term follow-up study in normoovulatory women.

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⁴Division of Endocrinology, Department of Internal Medicine, University Medical Center, Utrecht, The Netherlands

Abstract

CONTEXT: It has been hypothesized that a fixed interval exists between age at natural sterility and age at menopause. Both events show considerable individual variability, with a range of 20 yr. Correct prediction of age at menopause could open avenues of individualized prevention of age-related infertility and other menopause-related conditions, like cardiovascular disease and breast carcinoma.

OBJECTIVE: The aim of this study was to explore the ability of ovarian reserve tests to predict age at menopause.

DESIGN AND SETTING: We conducted a long-term follow-up study at an academic hospital.

PARTICIPANTS: A total of 257 normoovulatory women (age, 21-46 yr) were derived from three cohorts with highly comparable selection criteria.

INTERVENTIONS: Anti-Müllerian hormone (AMH), antral follicle count, and FSH were assessed at time 1 (T1). At time 2 (T2), approximately 11 yr later, cycle status (strictly regular, menopausal transition, or postmenopause) and age at menopause were inventoried.

MAIN OUTCOME MEASURES: Accuracy of the ovarian reserve tests in predicting time to menopause was assessed by Cox regression, and a nomogram was constructed for the relationship between age-specific AMH concentrations at T1 and age at menopause.

RESULTS: A total of 48 (19%) women had reached postmenopause at T2. Age, AMH, and antral follicle count at T1 were significantly related with time to menopause (P <0.001) and showed a good percentage of correct predictions (C-statistic, 0.87, 0.86, and 0.84, respectively). After adjusting for age, only AMH added to this prediction (C-statistic, 0.90). From the constructed nomogram, it appeared that the normal distribution of age at menopause will shift considerably, depending on the individual age-specific AMH level.

CONCLUSIONS: AMH is highly predictive for timing of menopause. Using age and AMH, the age range in which menopause will subsequently occur can be individually calculated.
Reproductive and lifestyle determinants of anti-Müllerian hormone in a large population-based study.

AUTHORS: Dólleman M1, Verschuren WM, Eijkemans MJ, Dollé ME, Jansen EH, Broekmans FJ, van der Schouw YT.

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Abstract

CONTEXT: Anti-müllerian hormone (AMH) is an ovarian reserve marker that is increasingly applied in clinical practice as a prognostic and diagnostic tool. Despite increased use of AMH in clinical practice, large-scale studies addressing the influence of possible determinants on AMH levels are scarce.

OBJECTIVE: We aimed to address the role of reproductive and lifestyle determinants of AMH in a large population-based cohort of women.

DESIGN: In this cross-sectional study, age-specific AMH percentiles were calculated using general linear modeling with CG-LMS (Cole and Green, Lambda, Mu, and Sigma model, an established method to calculate growth curves for children).

SETTING: Women from the general community participating in the Doetinchem Cohort study were assessed.

PARTICIPANTS: Two thousand three hundred twenty premenopausal women were included.

MAIN OUTCOME MEASURE: The effect of female reproductive and lifestyle factors on shifts in age-specific AMH percentiles was studied.

RESULTS: In comparison to women with a regular menstrual cycle, current oral contraceptive (OC) users, women with menstrual cycle irregularity, and pregnant women had significantly lower age-specific AMH percentiles (for OC use, 11 percentiles lower; for cycle irregularity, 11 percentiles lower; and for pregnancy, 17 percentiles lower [P value for all < .0001]). Age at menarche and age at first childbirth were not associated with the age-specific AMH percentile. Higher parity was associated with 2 percentiles higher age-specific AMH (P = .02). Of the lifestyle factors investigated, current smoking was associated with 4 percentiles lower age-specific AMH percentiles (P = .02), irrespective of the smoking dose. Body mass index, waist circumference, alcohol consumption, physical exercise, and socioeconomic status were not significantly associated with age-specific AMH percentiles.

CONCLUSIONS: This study demonstrates that several reproductive and lifestyle factors are associated with age-specific AMH levels. The lower AMH levels associated with OC use and smoking seem reversible, as effects were confined to current use of OC or cigarettes. It is important to give careful consideration to the effect of such determinants when interpreting AMH in a clinical setting and basing patient management on AMH.
Anti-Mullerian-hormone levels during pregnancy and postpartum.

AUTHORS: Köninger A¹, Kauth A, Schmidt B, Schmidt M, Yerlikaya G, Kasimir-Bauer S, Kimmig R, Birdir C.

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Abstract

BACKGROUND: The number of unintentionally childless couples is increasing as more couples seek to conceive for the first time in the third or fourth decade of the woman’s life. Determination of ovarian reserve is an essential component of infertility assessment. The Anti-Müllerian-Hormone (AMH) seems to be the most reliable predictor of ovarian reserve. In this study we analyzed AMH in a cohort of pregnant women without fertility impairment to determine age-dependent decline and possible AMH fluctuations during pregnancy and postpartum.

METHODS: A total of 554 healthy women aged 16 to 47 years without history of infertility or previous surgery on the ovaries were enrolled in the study between 1995 and 2012. In 450 women, a single measurement of AMH was taken during pregnancy, allowing for cross sectional analysis of trimester- and age-related differences in AMH levels. For another 15 women longitudinal data on AMH levels for all trimesters was recorded. In addition, for 69 women AMH was measured at the time just before and after delivery, and for another 20 AMH was measured just before delivery and once on each of the first four days after delivery. We used AMH-Gen-II ELISA (Beckman Coulter, Immunotech, Webster, USA) for the assessment of AMH levels. Non-parametric statistical tests were used to compare AMH levels between age groups, trimesters and postpartum.

RESULTS: Comparison between the trimesters revealed a significant difference in AMH values at each trimester (first trimester: 1.69 ng/ml (IQR 0.71-3.10), second trimester: 0.8 ng/ml (IQR 0.48-1.41), third trimester: 0.5 ng/ml (IQR 0.18-1.00)). AMH significantly dropped during the course of pregnancy and immediately after delivery, whereas an increase was observed over the first four days postpartum. Women, greater than or equal to 35 years, showed significant lower AMH levels than those <35 years across all trimesters.

CONCLUSIONS: AMH levels decrease during pregnancy. The decline in AMH levels during pregnancy indicates ovarian suppression. AMH levels recover quickly after delivery. AMH levels assessed in pregnant women are not an accurate indicator of ovarian reserve, since AMH levels during pregnancy seem not to be independent of gestational age.
Anti-Müllerian Hormone, Follicle-stimulating Hormone, Antral Follicle Count, and Clinical Findings as Predictive Markers of Menopause in Late Reproductive-aged Women.

AUTHORS: Sun Mie Kim¹,², Seok Hyun Kim¹,³, Jung Ryeol Lee¹, Byung Chul Jee¹,⁴, Chang Suk Suh¹,³,⁴, Joong Yeup Lee¹,⁵, Ki Chul Kim⁵, Do Yeong Hwang⁵, Jung Gu Kim¹, Shin Yong Moon¹,³

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Abstract
Objective: To assess the efficiency of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol, antral follicle count (AFC), endometrial thickness (EMT), and clinical findings as predictive markers of menopause in late reproductive-aged Korean women.

Methods: A cohort of 104 women, aged 45 to 55 years in their menopausal transition were selected. The participants were assessed twice (T1 and T2) at a mean interval of 13.1 months. At each time, their menstrual history was determined; pelvic ultrasonography was performed to evaluate AFC and EMT; blood sampling was done. A logistic regression analysis using the SPSS ver. 17.0 was performed, with the outcome measure of menopause at T2.

Results: Of the 104 participants, 33 were postmenopausal based on their menstrual history at T2. Compared with women who stayed in the menopausal transition period, those who became postmenopausal at T2 differed significantly with regard to the following factors at T1: FSH, estradiol, EMT, AFC, days from the last menstrual cycle, and interval between the last 2 cycles. However, AMH levels were not different between the groups. Of all the parameters, a longer number of days from the last menstrual cycle and time interval between the last 2 cycles were significantly associated with the occurrence of menopause.

Conclusion: This study indicates that AMH is not a predictive marker of menopause in late reproductive-aged women over a relatively short timeframe (range, 0.5 to 2.5 years). Time since the last menstruation at T1 was a better predictor of menopause.
Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging.


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Abstract

OBJECTIVE: The aim of this article is to summarize the recommended updates to the 2001 Stages of Reproductive Aging Workshop (STRAW) criteria. The 2011 STRAW + 10 reviewed advances in understanding of the critical changes in hypothalamic-pituitary-ovarian function that occur before and after the final menstrual period.

METHODS: Scientists from five countries and multiple disciplines evaluated data from cohort studies of midlife women and in the context of chronic illness and endocrine disorders on change in menstrual, endocrine, and ovarian markers of reproductive aging including antimüllerian hormone, inhibin-B, follicle-stimulating hormone, and antral follicle count. Modifications were adopted by consensus.

RESULTS: STRAW + 10 simplified bleeding criteria for the early and late menopausal transition, recommended modifications to criteria for the late reproductive stage (Stage -3) and the early postmenopause stage (Stage +1), provided information on the duration of the late transition (Stage -1) and early postmenopause (Stage +1), and recommended application regardless of women’s age, ethnicity, body size, or lifestyle characteristics.

CONCLUSIONS: STRAW + 10 provides a more comprehensive basis for assessing reproductive aging in research and clinical contexts. Application of the STRAW + 10 staging system should improve comparability of studies of midlife women and facilitate clinical decision making. Nonetheless, important knowledge gaps persist, and seven research priorities are identified.
Antimüllerian hormone (AMH) not only a marker for prediction of ovarian reserve.

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Abstract
The main characteristics of the Antimüllerian hormone from the points of view of biochemistry, molecular genetics, physiological functions and importance for diagnostics in reproductive endocrinology and related biomedical fields are reviewed. The role of the hormone in male and female development, its participation in oocyte maturation including selection of a dominant follicle are summarized, as well as its changes under various pathological situations in both sexes. The physiological changes of serum AMH levels in the life span in both sexes and their alterations under various pathological conditions are provided, too.
PATHOPHYSIOLOGY

“Beckman Coulter’s AMH assay can predict long-term ovarian function after chemotherapy.”

Prof. Richard A. Anderson, BSc, Ph.D., MD FRCOG
Consultant in Reproductive Medicine, Royal Infirmary of Edinburgh
Professor of Clinical Reproductive Science, University of Edinburgh
Edinburgh, Scotland
Serum Müllerian inhibiting substance/anti-Müllerian hormone levels in patients with adult granulosa cell tumors directly correlate with aggregate tumor mass as determined by pathology or radiology.

AUTHORS: Chang HL1, Pahlavan N1, Halpern EF2, MacLaughlin DT1.

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Abstract

OBJECTIVES: Granulosa cell tumors (GCTs) comprise 2–5% of ovarian tumors. Serum Müllerian Inhibiting Substance (MIS, also known as anti-Müllerian hormone, or AMH) levels have been validated as a marker of GCT recurrence and progression. There has been little correlation between serum MIS/AMH levels and several clinical parameters in GCTs, including tumor burden. We have performed a retrospective review correlating aggregate tumor mass as reported by pathologic examination or by radiology with serum MIS/AMH levels drawn on the date of examination.

METHODS: We retrospectively identified 32 GCT patients at our institution over the last 15 years who had serum MIS/AMH measurements. Patients who had serum MIS/AMH measurements within three days of surgery or on the same day as abdominal computerized tomography scan (CT) or magnetic resonance imaging (MRI) were further evaluated.

RESULTS: We found a significant direct correlation between patient serum MIS/AMH levels and gross aggregate tumor mass determined by pathology (slope = 15.4 ± 6.06, r = 0.65, P < 0.04) or by radiographic aggregate tumor mass for all data points identified (slope = 0.07 ± 0.03, r = 0.33, P < 0.04) and after correcting for selection bias (slope = 1.45 ± 0.17, r = 0.93, P < 0.01). We also identified a significant difference between serum MIS/AMH levels between samples drawn the same day as negative and positive abdominal CT or MRI scans (8.16 ± 1.54 vs. 158.7 ± 32.2 ng/ml, P < 0.0001).

CONCLUSIONS: These data indicate a significant direct correlation between serum MIS/AMH levels and both gross and radiographic aggregate tumor mass in GCT patients. Together with the current literature, the present data argue for a more prominent role for serum MIS/AMH in the management of GCTs.

The anti-Müllerian hormone and ovarian cancer.

AUTHORS: La Marca A, Volpe A.

CENTER: Mother–Infant Department, Institute of Obstetrics and Gynecology, University of Modena and Reggio Emilia, Modena, Italy

Abstract

The anti-Müllerian hormone (AMH), which is produced by fetal Sertoli cells, is responsible for regression of Müllerian ducts, the anlagen for uterus and Fallopian tubes, during male sex differentiation. Ovarian granulosa cells also secrete AMH from late in fetal life. The patterns of expression of AMH and its type II receptor in the post-natal ovary indicate that AMH may play an important role in ovarian folliculogenesis. Recent advances in the physiological role of AMH have stimulated interest in the significance of AMH as a diagnostic marker and therapeutic agent for ovarian cancer. Currently, AMH has been shown to be a circulating marker specifically for granulosa cell tumour (GCT). Its diagnostic performance seems to be very good, with a sensitivity ranging between 76 and 93%. In patients treated for GCT, AMH may be used post-operatively as marker for the efficacy of surgery and for disease recurrence. Based on the physiological inhibitory role of AMH in the Müllerian ducts, it has been proposed that AMH may inhibit epithelial ovarian cancer cell both in vitro and in vivo. These observations will be the basis for future research aiming to investigate the possible clinical role of AMH as neo-adjuvant, or most probably adjuvant, therapy for ovarian cancer.
Pretreatment serum anti-Müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer.

AUTHORS: Anderson RA¹, Cameron DA².

CENTER: ¹Division of Reproduction and Developmental Sciences and Medical Research, Council Human Reproductive Sciences Unit, Centre for Reproductive Biology, University of Edinburgh, Edinburgh, United Kingdom
²Edinburgh Breast Unit and Edinburgh University Cancer Research Centre, Western General Hospital, Edinburgh, United Kingdom

Abstract

CONTEXT: Administration of chemotherapy to premenopausal women shortens their reproductive lifespan by depleting nonrenewable oocytes. Preservation of fertility is a priority for many such women, and identification of women at risk of infertility is therefore important. However, age is the only patient characteristic currently recognized to be predictive of long-term ovarian function after chemotherapy.

OBJECTIVE: Our objective was to assess markers of ovarian reserve and age as long-term predictors of ovarian function after chemotherapy.

DESIGN AND SETTING: We conducted a prospective, longitudinal study at a university hospital and research institute.

PATIENTS: Patients included women who were premenopausal at the time of diagnosis of early breast cancer.

MAIN OUTCOME MEASURES: Ovarian function was assessed at 5-year follow-up in relation to pretreatment hormonal and ultrasound markers of ovarian reserve.

RESULTS: Forty-two women received (neo-)adjuvant chemotherapy. Continuing menses 4–5 years after diagnosis closely reflected ovarian activity as assessed by a range of serum markers, including estradiol, inhibin B, FSH, and anti-Müllerian hormone (AMH). Pretreatment serum AMH, FSH, antral follicle count, and age predicted late ovarian activity by univariate analysis. However, only AMH was predictive in a multivariate logistic regression (odds ratio = 13.0; 95% confidence interval = 2.5–66.7); 0.71 ng/ml gave peak likelihood ratio of 7.0 with 54% sensitivity and 92% specificity. Bone mineral density fell over 4–5 years after diagnosis with greater loss in women with lower ovarian activity. Higher pretreatment AMH was associated with lower bone mineral density at both lumbar spine and hip at 5 years (P <0.02).

CONCLUSIONS: Measurement of AMH at cancer diagnosis predicts long-term ovarian function after chemotherapy. Use of this in clinical practice may allow better prediction of chemotherapy-related risk to future fertility.
Pretreatment anti-Müllerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer.

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Abstract

AIM: Improving survival for women with early breast cancer (eBC) requires greater attention to the consequences of treatment, including risk to ovarian function. We have assessed whether biochemical markers of the ovarian reserve might improve prediction of chemotherapy related amenorrhoea.

METHODS: Women (n=59, mean age 42.6 years ([range 23.3-52.5]) with eBC were recruited before any treatment. Pretreatment ovarian reserve markers (anti-Müllerian hormone [AMH], follicle-stimulating hormone [FSH], inhibin B) were analysed in relation to ovarian status at 2 years.

RESULTS: Pretreatment AMH was significantly lower in women with amenorrhoea at 2 years (4.0 ± 0.9 pmol/L versus 17.2 ± 2.5, P<0.0001), but FSH and inhibin B did not differ between groups. By logistic regression, pretreatment AMH, but not age, FSH or inhibin B, was an independent predictor of ovarian status at 2 years (P=0.005; odds ratio 0.013). We combined these data with a similar cohort (combined n=75); receiver-operator characteristic analysis for AMH gave area under curve (AUC) of 0.90 (95% confidence interval (CI) 0.82-0.97). A cross-validated classification tree analysis resulted in a binary classification schema with sensitivity 98.2% and specificity 80.0% for correct classification of amenorrhoea.

CONCLUSION: Pretreatment AMH is a useful predictor of long term post chemotherapy loss of ovarian function in women with eBC, adding significantly to the only previously established individualising predictor, i.e. age. AMH measurement may assist decision-making regarding treatment options and fertility preservation procedures.
Anti-Müllerian hormone and inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors.

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Abstract

BACKGROUND: In late reproductive-aged breast cancer survivors, there is a need for real-time biomarkers of postchemotherapy ovarian function. The objective was to determine whether anti-Müllerian hormone (AMH) and inhibin B are such biomarkers. The authors tested whether AMH and inhibin B were impacted by breast cancer treatment by comparing cancer survivors to age-matched control women and determined the association between these hormones and postchemotherapy menstrual pattern.

METHODS: Breast cancer patients (n = 127) with American Joint Committee on Cancer stage I to III disease who were premenopausal at diagnosis were enrolled postchemotherapy and observed. The primary endpoint was chemotherapy-related amenorrhea (CRA) (≥ 12 months of amenorrhea after chemotherapy). Matched pair analyses compared AMH, inhibin B, and follicle-stimulating hormone (FSH) levels between cancer and age-matched control subjects. Associations between hormones, CRA status, and change in CRA status over time were assessed.

RESULTS: The median age of the patients at chemotherapy was 43.2 years (range, 26.7-57.8 years). At enrollment, median follow-up since chemotherapy was 2.1 years, and 55% of subjects had CRA. Compared with age-matched controls, cancer subjects had significantly lower AMH (P = .004) and inhibin B (P < .001) and higher FSH (P < .001). AMH (P = .002) and inhibin B (P = .001) were found to be significantly associated with risk of CRA, even after controlling for FSH. AMH was significantly lower (P = .03) and FSH was significantly higher (P = .04) in menstruating subjects who developed subsequent CRA.

CONCLUSIONS: AMH and inhibin B are 2 additional measures of postchemotherapy ovarian function in late reproductive-aged breast cancer survivors. With further research and validation, these hormones may supplement limited current tools for assessing and predicting postchemotherapy ovarian function.
Anti-Müllerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results.

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Abstract
Susceptibility of the ovarian reserve to chemotherapy is highly variable from one patient to another and poorly documented. To better characterize the evolution of follicular depletion in patients treated for lymphoma, serum anti-Müllerian hormone (AMH) assay was used. A total of 30 young women (mean age 24 years) were prospectively recruited before initiation of chemotherapy for lymphoma. They were assigned either to an Adriamycin, bleomycin, vinblastine and dacarbazine protocol (ABVD group) or to a protocol that included cyclophosphamide (non-ABVD group). AMH assays were performed before and during chemotherapy, and then every 3 months after the end of treatment for a period of 1 year. In all patients, AMH concentrations fell drastically just after the start of chemotherapy and were close to the detection limit at the end of the treatment. In the ABVD group, AMH concentrations increased from the third month after the end of chemotherapy and returned to pretreatment values 12 months after the end of chemotherapy. Conversely, no significant change was observed in the non-ABVD group throughout the follow-up period. In conclusion, longitudinal analysis of AMH during chemotherapy highlights differences between protocols that could contribute to an understanding of ovarian toxicity and, ultimately, be useful in fertility preservation counselling.

Antimüllerian hormone, the assessment of the ovarian reserve, and the reproductive outcome of the young patient with cancer.

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Abstract
The accurate assessment of the ovarian reserve has long been a key goal in reproductive medicine. The recognition that serum antimüllerian hormone provides an indirect measure of the ovarian reserve has led to its rapid adoption in assisted conception, and wide exploration of its potential across the reproductive lifespan from the neonate to the menopause. In this short review we discuss its relationship with the ovarian reserve in its varied meanings, and in various contexts. These include in childhood and adolescence, and in the assessment of the impact of cancer therapy on the female reproductive tract. These therapies can adversely impact all aspects of female reproduction, including hypothalamic, pituitary, and ovarian hormonal activity, and the ability of the uterus to support a successful pregnancy.
Prediction of postchemotherapy ovarian function using markers of ovarian reserve.

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Abstract
BACKGROUND: Reproductive-aged women frequently receive both chemotherapy and endocrine therapy as part of their treatment regimen for early stage hormone receptor-positive breast cancer. Chemotherapy results in transient or permanent ovarian failure in the majority of women. The difficulty in determining which patients will recover ovarian function has implications for adjuvant endocrine therapy decision making. We hypothesized that pretreatment serum anti-Müllerian hormone (AMH) and inhibin B concentrations would predict for ovarian function following chemotherapy.

METHODS: Pre- and perimenopausal women aged 25-50 years with newly diagnosed breast cancer were enrolled. Subjects underwent phlebotomy for assessment of serum AMH, inhibin B, follicle-stimulating hormone, and estradiol prior to chemotherapy and 1 month and 1 year following completion of treatment. Associations among hormone concentrations, clinical factors, and biochemically assessed ovarian function were assessed.

RESULTS: Twenty-seven subjects were evaluable for the primary endpoint. Median age was 41. Twenty subjects (74.1%) experienced recovery of ovarian function within 18 months. Of the 26 evaluable subjects assessed prior to chemotherapy, 19 (73.1%) had detectable serum concentrations of AMH. The positive predictive value of a detectable baseline serum AMH concentration for recovery of ovarian function was 94.7%, and the negative predictive value was 85.7%. On univariate analysis, younger age and detectable serum AMH concentration at chemotherapy initiation were predictive of increased likelihood of recovery of ovarian function.

CONCLUSION: Prechemotherapy assessment of serum AMH may be useful for predicting postchemotherapy ovarian function. This finding has implications for decision making about adjuvant endocrine therapy in premenopausal women treated with chemotherapy.
Serum anti-Müllerian hormone levels remain stable throughout the menstrual cycle and after oral or vaginal administration of synthetic sex steroids.

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Abstract

OBJECTIVE: To investigate whether oral or vaginal administration of contraceptive hormones might affect anti-Müllerian hormone (AMH) levels.

DESIGN: Prospective trial with women recruited by advertisement. Women who wished contraception were randomized between oral or vaginal estroprogestative contraception, and those who did not choose contraception were included in the control group.

SETTING: Fertility clinic of a tertiary university hospital.

PATIENT(S): Twenty-four young, healthy volunteer women with regular cycles who had received no hormonal contraception for at least 3 months before the study.

INTERVENTION(S): Oral or vaginal estroprogestative contraception from day 5 to 25 of a menstrual cycle versus no contraception.

MAIN OUTCOME MEASURE(S): Intercycle and intracycle variations of serum AMH levels in normally ovulating volunteers and following the initiation of oral or vaginal estroprogestative contraception.

RESULT(S): Fluctuations of AMH levels observed during the menstrual cycle remained within cycle-to-cycle variability in cycling controls and in women receiving oral or vaginal contraception.

CONCLUSION(S): Our findings confirm that AMH levels remain steady during the menstrual cycle and indicate that they are unaffected by exogenous sex steroids used for contraception whether administered orally or vaginally.
Evaluation of serum anti-Mullerian hormone levels to assess the ovarian reserve in women with severe endometriosis.


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Abstract

OBJECTIVE: The aim of this study was to measure anti-Mullerian hormone (AMH) serum levels in women with severe endometriosis, in order to demonstrate the effect of the disease on ovarian reserve.

STUDY DESIGN: Prospective case-control study. One hundred and ninety-five patients were enrolled: 130 fertile patients (group A) and 65 patients with stage III and IV endometriosis, diagnosed by laparoscopy and histological examination (group B). AMH serum levels were measured in both groups and were compared using Student’s t-test.

RESULTS: The two groups were homogenous for main demographic data. Group B had statistically significantly lower mean AMH serum levels (0.97±0.59ng/ml) than group A (1.72±0.63ng/ml) (p=0.001).

CONCLUSIONS: This study is a demonstration of the damage of endometriosis on ovarian reserve, leading to a form of incipient ovarian failure, which is considered as an early sign of advanced ovarian depletion in young women. These findings suggest that AMH could be used in the follow-up of patients with endometriosis, in order to assess promptly the decrease of ovarian reserve.
Serum anti-Müllerian hormone levels in the main phenotypes of polycystic ovary syndrome.

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Abstract

OBJECTIVE: To characterize the difference in circulating anti-Müllerian hormone (AMH) levels between the main polycystic ovary syndrome (PCOS) phenotypic groups and evaluate the role of AMH in predicting the severity of PCOS.

STUDY DESIGN: Cross-sectional, retrospective study. A total of 251 women were divided into four groups based on the main features of PCOS, as follows: Group 1 (polycystic ovarian morphology [PCOM]+/oligo-anovulation [OA]+/hyperandrogenism [HA]+), Group 2 (PCOM+/OA+/HA-), Group 3 (PCOM+/OA-/HA+), and Group 4 (PCOM-/OA+/HA+). AMH and other hormone levels were measured in serum. The main outcome was serum AMH concentrations in the main phenotypes of PCOS.

RESULT(S): The mean serum AMH levels were 9.50±6.1 ng/mL in Group 1; 8.02±6.2 ng/mL in Group 2; 6.12±3.6 ng/mL in Group 3; and 3.06±2.4 ng/mL in Group 4. Circulating AMH levels in Group 1 (PCOM+/OA+/HA+) were three times higher than those in Group 4 (PCOM-/OA+/HA+).

CONCLUSIONS: The highest AMH levels were found in cases where all three main diagnostic criteria existed. AMH levels correlate best with PCOM. In addition, oligo-anovulation contributes to increased AMH levels. Hyperandrogenism criteria were found to have less influence on AMH levels. AMH levels seem to have a diagnostic role in determining the severity of PCOS.
The role of AMH in anovulation associated with PCOS: a hypothesis.

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Abstract
Polycystic ovary syndrome (PCOS) is the most common cause of infertility due to anovulation. Despite its prevalence, the precise cause of the anovulation is yet to be clearly defined. There is an increased number of pre-antral and antral follicles in the polycystic ovary, many of which individually produce increased amounts of anti-Müllerian hormone (AMH) compared with those in the normal ovary. In this article, it is hypothesized that the high AMH concentrations present in women with PCOS play an integral role in causing anovulation due to its inhibitory influence on the actions of follicle-stimulating hormone, which normally promotes follicular development from the small antral to the ovulatory stage.
Can anti-Mullerian hormone predict the diagnosis of polycystic ovary syndrome? A systematic review and meta-analysis of extracted data.

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Abstract

CONTEXT: Existing biochemical tests for polycystic ovary syndrome (PCOS) have poor sensitivity and specificity. Many women with PCOS have high anti-Müllerian hormone (AMH) concentrations; thus, this may be a useful addition to the diagnostic criteria.

OBJECTIVE: A systematic literature review was performed to assess the true accuracy of AMH in the prediction of PCOS and to determine the optimal diagnostic threshold.

DATA SOURCES: Published and gray literature were searched for all years until January 2013.

STUDY SELECTION: Observational studies defining PCOS according to the Rotterdam criteria and assessing the value of AMH in diagnosing PCOS were selected. Ten studies of the initial 314 hits reporting AMH values in the diagnosis of PCOS were included in the meta-analysis and the construction of the summary receiver-operating characteristic curve. Four studies that plotted individual AMH serum levels of women with PCOS and controls on graphs were selected for individual data extraction.

DATA EXTRACTION: Two researchers independently assessed the abstracts resulted from the initial search against the inclusion criteria, graded the papers for selection and verification biases, and selected the papers that assessed the value of AMH in diagnosing PCOS. Data were extracted from 4 studies with the plotted individual data on graphs with the help of computer software.

DATA SYNTHESIS: The meta-analysis of the extracted data demonstrated the specificity and sensitivity in diagnosing PCOS in the symptomatic women of 79.4% and 82.8%, respectively, for a cutoff value of AMH of 4.7 ng/mL. The area under the curve was 0.87 (95% confidence interval 0.83-0.92), identical with the area under the curve of 0.87 for the summary receiver-operating characteristic curve involving 10 separate studies.

CONCLUSIONS: AMH may be a useful initial diagnostic test for PCOS subject to validation in prospective population cohorts.
Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society.

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Abstract

BACKGROUND: The diagnosis of polycystic ovary syndrome (PCOS) relies on clinical, biological and morphological criteria. With the advent of ultrasonography, follicle excess has become the main aspect of polycystic ovarian morphology (PCOM). Since 2003, most investigators have used a threshold of 12 follicles (measuring 2-9 mm in diameter) per whole ovary, but that now seems obsolete. An increase in ovarian volume (OV) and/or area may also be considered accurate markers of PCOM, yet their utility compared with follicle excess remains unclear.

METHODS: Published peer-reviewed medical literature about PCOM was searched using PubMed.gov online facilities and was submitted to critical assessment by a panel of experts. Studies reporting antral follicle counts (AFC) or follicle number per ovary (FNPO) using transvaginal ultrasonography in healthy women of reproductive age were also included. Only studies that reported the mean or median AFC or FNPO of follicles measuring 2-9 mm, 2-10 mm or <10 mm in diameter, or visualized all follicles, were included.

RESULTS: Studies addressing women recruited from the general population and studies comparing control and PCOS populations with appropriate statistics were convergent towards setting the threshold for increased FNPO at ≥25 follicles, in women aged 18-35 years. These studies suggested maintaining the threshold for increased OV at ≥10 ml. Critical analysis of the literature showed that OV had less diagnostic potential for PCOM compared with FNPO. The review did not identify any additional diagnostic advantage for other ultrasound metrics such as specific measurements of ovarian stroma or blood flow. Even though serum concentrations of anti-Müllerian hormone (AMH) showed a diagnostic performance for PCOM that was equal to or better than that of FNPO in some series, the accuracy and reproducibility issues of currently available AMH assays preclude the establishment of a threshold value for its use as a surrogate marker of PCOM. PCOM does not associate with significant consequences for health in the absence of other symptoms of PCOS but, because of the use of inconsistent definitions of PCOM among studies, this question cannot be answered with absolute certainty.

CONCLUSIONS: The Task Force recommends using FNPO for the definition of PCOM setting the threshold at ≥25, but only when using newer technology that affords maximal resolution of ovarian follicles (i.e. transducer frequency ≥8 MHz). If such technology is not available, we recommend using OV rather than FNPO for the diagnosis of PCOM for routine daily practice but not for research studies that require the precise full characterization of patients. The Task Force recognizes the still unmet need for standardization of the follicle counting technique and the need for regularly updating the thresholds used to define follicle excess, particularly in diverse populations. Serum AMH concentration generated great expectations as a surrogate marker for the follicle excess of PCOM, but full standardization of AMH assays is needed before they can be routinely used for clinical practice and research. Finally, the finding of PCOM in ovulatory women not showing clinical or biochemical androgen excess may be inconsequential, even though some studies suggest that isolated PCOM may represent the milder end of the PCOS spectrum.
Serum AMH levels in women with a history of preeclampsia suggest a role for vascular factors in ovarian aging.

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Abstract

CONTEXT: The association between early menopause and vascular disease as a possible causative factor has recently received attention. Preeclampsia (PE) is associated with future cardiovascular risk factors, and this premature vascular aging potentially modifies the ovarian aging process.

OBJECTIVE: The purpose of this study was to assess whether women with a history of PE have lower anti-Müllerian hormone (AMH) levels than women with normotensive pregnancies.

DESIGN: This was a retrospective cohort study.

SETTING: The study was conducted in a tertiary referral center.

PATIENTS: Clinical data and blood samples of participants in the Preeclampsia Risk EValuation in FEMales study were used (336 women with a history of PE and 329 women after a normotensive pregnancy).

INTERVENTIONS: There were no interventions.

MAIN OUTCOME MEASURES: The relative decrease in AMH levels was assessed after a median follow-up of 10.5 years.

RESULTS: The mean AMH level was 2.00 ± 1.87 μg/L in the PE group compared with 2.26 ± 2.56 μg/L in the reference group. Linear regression analysis with censoring for undetectable AMH levels, adjusted for age, smoking, and hormonal contraceptive use, showed a relative reduction in AMH levels of 20.9% at any age (fold change 0.79, 95% confidence interval, 0.67-0.94).

CONCLUSIONS: We demonstrate that women with a history of PE have significantly lower AMH levels than women with normotensive pregnancies. Calculations based on a reference population indicate advancement of reproductive age of approximately 1.5 years. Because PE is considered a manifestation of impaired vascular health, these results support the hypothesis that compromised vascular health could act as a causative mechanism in early ovarian aging.
Anti-müllerian hormone and sertoli cell function in paediatric male hypogonadism.

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Abstract
In the prepubertal male, Sertoli cells are the most active testicular cell population. Without stimulation tests, prepubertal hypogonadism can only be evidenced if Sertoli cell function is assessed. Anti-müllerian hormone (AMH) is a distinctive marker of the prepubertal Sertoli cell. Serum AMH is high from fetal life until puberty. In postnatal life, AMH testicular production is stimulated by FSH and potently inhibited by androgens. In anorchid patients, AMH is undetectable. In prepubertal males with fetal- or childhood-onset primary or central hypogonadism affecting the whole gonad, serum AMH is low. Conversely, when hypogonadism only affects Leydig cells (i.e., LH/human chorionic gonadotrophin receptor or steroidogenic enzyme defects), serum AMH is normal/high. AMH is also normal/high in patients with androgen insensitivity. In patients of pubertal age with central hypogonadism, AMH is low for Tanner stage - reflecting lack of FSH stimulus, - but high for age - reflecting lack of testosterone inhibitory effect. FSH treatment results in serum AMH rise, whereas human chorionic gonadotrophin treatment increases testosterone levels which inhibit AMH production. In conclusion, AMH determination is helpful in assessing gonadal function, without need for stimulation tests, and orientates the aetiological diagnosis of paediatric male hypogonadism. Furthermore, serum AMH is an excellent marker of FSH and androgen action in the testis.
1999
Beckman Coulter / Immunotech launches first AMH assay

2004
DSL launches AMH ELISA

2005
Beckman Coulter acquires DSL

2009
Beckman Coulter launches AMH Gen II

1999-2014
Over 2000 AMH clinical publications

2014
Beckman Coulter launches Access AMH
Development of a second generation anti-Müllerian hormone (AMH) ELISA.

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Abstract

AMH is a glycoprotein dimer composed of two 72 kDa monomers linked by disulfide bridges. It belongs to the transforming growth factor-β family. AMH performs various physiological functions. In males, AMH is secreted by the Sertoli cells of the testis. During embryonic development, AMH is responsible for Müllerian duct regression. AMH continues to be produced by the testicles until puberty and then decreases slowly to residual post-puberty values. In females, AMH is produced in small amounts by ovarian granulosa cells after birth, until menopause, and then becomes undetectable. A two-step, sandwich-type enzymatic microplate assay has been developed to measure AMH levels in 20 μL of sample in less than 3h. AMH calibrators range from 0.2 to 28 ng/mL. The antibodies used in the assay bind to the mature region of AMH, which is more stable to proteolysis compared to prohormone region. The AMH Gen II assay (Beckman Coulter, Inc., Webster, Texas) was standardized to the Immunotech (IOT, Beckman Coulter, Inc., Marseilles, France) AMH assay. AMH Gen II, when compared to IOT using 120 serum samples in the range of 0–20.4 ng/mL yielded a correlation coefficient of 0.98 and a slope of 1.0. Total imprecision, calculated on four samples over 40 runs, four replicates per run, between two lots using CLSI EP5-A guidelines, was 5.7% at 3.8 ng/mL, 7.7% at 4.4 ng/mL, 5.8% at 14 ng/mL and 5.3% at 16.4 ng/mL. The average analytical sensitivity calculated by the interpolation of the mean plus two standard deviations of 16 replicates of the zero calibrator on two independent lots was 0.08 ng/mL. Dilution and spiking studies showed an average recovery of 91–110%. Lot-to-lot comparison of two independent lots testing 38 serum samples (1.5–33 ng/mL range) yielded a slope of 1.01, intercept of −0.08 ng/mL and r of 0.99. When potential interferents (hemoglobin, triglycerides, and bilirubin) were added at two times the physiological concentrations, AMH concentrations were within ±10% of the control. A highly specific and reproducible microplate AMH Gen II assay has been developed to standardize the measurement of AMH between methods. The performance of the AMH Gen II assay is ideal for investigation into the physiologic roles of AMH in men and women.
A multicentre evaluation of the new Beckman Coulter anti-Müllerian hormone immunoassay (AMH Gen II).


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Abstract

BACKGROUND: The measurement of anti-Müllerian hormone (AMH) has been by two commercial enzyme-linked immunosorbent (ELISA) assays: Diagnostics Systems Laboratory (DSL 10-14400) and Immunotech (A11893 IVD EU only). Beckman Coulter has developed a new assay for AMH (AMH Gen II A79765), which uses the DSL antibodies but is standardized to the Immunotech calibration. As a result, comparative data are urgently required between the old DSL assay and its replacement AMH Gen II.

METHODS: An evaluation of the AMH Gen II assay was performed at three sites, each with extensive experience of measuring circulating AMH in the adult female. Results were compared with the original DSL ELISA assay. The analysis was performed on a total of 271 patients’ samples, approximately 90 at each site.

RESULTS: Performance characteristics were evaluated for the AMH Gen II assay. Linearity was acceptable with observed values close to the expected (mean recovery 106.3%). The functional sensitivity (20% coefficient of variation), calculated from precision profile data, was 1.5 pmol/L. Within- and between-batch imprecision, assessed over the concentration range of 5–70 pmol/L, were 5.3–11.4% and 3.8–17.3%, respectively. There was good agreement between assays with a Bablok-Passing regression equation AMH Gen II = 1.40 DSL–0.62 pmol/L, r = 0.96, n = 271.

CONCLUSIONS: Our results demonstrate that similar precision and excellent between-assay agreement should be obtained when laboratories change from the DSL to the AMH Gen II ELISA and they should expect an increase in AMH values of approximately 40%.
Clinical uses of anti-Müllerian hormone assays: pitfalls and promises.


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Abstract

OBJECTIVE: To investigate whether the controversy about fluctuations of anti-Müllerian hormone (AMH) levels during the menstrual cycle results from differences between the immunoassays currently available: the Beckman Coulter ImmunoTech kit (Fullerton, CA) and the Diagnostic Systems Laboratories kit (Webster, TX).

DESIGN: Prospective trial.

SETTING: Fertility clinics of two tertiary university hospitals.

PATIENT(S): One hundred sixty-eight blood samples from three different populations. Serial samples at set intervals from the LH surge were taken in a fourth population of 10 volunteers.

INTERVENTION(S): We remeasured AMH levels by using the Diagnostic Systems Laboratories kit in 168 blood samples in which AMH initially had been measured by using the Beckman Coulter assay. We also conducted serial AMH measurements (n = 7) during the menstrual cycle of 10 women.

MAIN OUTCOME MEASURE(S): Linear regression of AMH levels determined by using 2 different assays and analysis of variance of serial measurements in the menstrual cycle.

RESULT(S): We found a linear relationship between the 2 methods, with a correlation coefficient of 0.88. When repeated individual AMH measures were longitudinally analyzed in relation to the LH surge, a slight but significant decrease was observed after ovulation.

CONCLUSION(S): Differences in AMH fluctuations during the menstrual cycle reported in recent publications do not result from the use of different AMH assays. The changes in AMH levels after ovulation are slight, yet statistically significant. However, the fluctuations observed are smaller than intercycle variability and therefore are not clinically relevant as far as AMH measurements for clinical purposes are concerned. In daily practice, AMH therefore can be measured anytime during the menstrual cycle.

Pre-mixing serum samples with assay buffer is a prerequisite for reproducible anti-Müllerian hormone measurement using the Beckman Coulter Gen II assay.

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Abstract
STUDY QUESTION: Does pre-mixing stored serum samples with assay buffer improve the reproducibility of the Beckman Gen II assay for anti-Müllerian hormone (AMH)?

SUMMARY ANSWER: Pre-mixing serum samples with assay buffer is a prerequisite for reproducible measurement of AMH in serum using the Beckman Coulter Gen II assay.

WHAT IS KNOWN ALREADY: Discrepancies in the results obtained from AMH assays have raised doubts concerning the clinical utility of measuring AMH. Sample storage conditions may be responsible for the lack of reproducibility of results obtained from the Gen II kit.

STUDY DESIGN, SIZE, DURATION: This was a prospective study in which serum samples were stored at three different temperatures and assayed for AMH at times 0, 4, 8, 12, 24, 48 h and 1 or 2 weeks after collection. Volunteers (n = 28) were healthy non-pregnant and early pregnant women aged 22-41 years. Anonymized long-term stored samples (n = 42, stored at -20° for 2 weeks) from fertility clinic attendees were also included. For determining the reference range, 179 samples from healthy pregnant women presenting for first trimester screening were used.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Thirty separate assays were performed by two operators using four different Gen II kit lots with both kit and in-house quality controls (QCs) included in each assay. In addition to the standard protocol, a modified protocol (pre-mixing samples with assay buffer) was used for selected sample groups.

MAIN RESULTS AND THE ROLE OF CHANCE: In non-pregnant women, AMH concentrations remained unchanged in serum stored for up to 8 h at room temperature, -20 and -80°C. At room temperature, levels started to rise by 24 h, increasing by up to 29% of the time 0 h value by 48 h and 26% after 1 week. Significant changes versus baseline (time 0 h) in measured AMH concentration were also observed after storage at -20 and -80°C (only at the 12 h time point). In the pregnant group, there was a 50% increase above baseline in samples stored for 48 h at room temperature. When samples were pre-mixed with assay buffer, AMH concentrations showed a consistent increase versus the standard assay in both non-pregnant (29%) and pregnant (280%) groups, regardless of storage conditions and duration, but concentrations remained constant during long-term storage (2 weeks). Stored fertility clinic patient samples also exhibited stability of AMH values after a consistent 2-fold increase following pre-mixing. Kit QCs were consistent over 30 weeks using either standard or modified protocols while the in-house pooled serum QC rose over time unless using the modified protocol. Overall, there was a 2-fold increase in medians in the pre-mixed reference range, with the biggest increase observed in the oldest age bracket (41-45 years, 3.4-fold).

LIMITATIONS, REASONS FOR CAUTION: The cause of the observed instability of AMH in stored serum samples requires further investigation, which is outside the scope of this publication. A larger and wider population study is necessary for a more reliable and clinically relevant reference range.

WIDER IMPLICATIONS OF THE FINDINGS: Our study has confirmed previous findings of lack of consistency in AMH concentrations when measured with the Gen II assay. Pre-mixing serum samples with assay buffer gave higher but also the most consistent results regardless of storage conditions; therefore, we propose that all serum samples for AMH assay should be pre-mixed with assay buffer. Furthermore, clinical laboratories that offer AMH measurement as part of the assessment of endocrinopathies, such as polycystic ovary syndrome or premature ovarian failure, or for management of ovulation induction as part of assisted reproduction, must re-establish their own normal ranges using the modified method.

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Maximizing the clinical utility of antimüllerian hormone testing in women’s health.

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Abstract

PURPOSE OF REVIEW: To provide an update on the latest clinical applications of serum antimüllerian hormone (AMH) testing with practical approaches to mitigate the impact of significant variability in AMH results.

RECENT FINDINGS: Recent studies continue to demonstrate that AMH is the best single serum test for ovarian response management with, at most, a weak-to-moderate age-independent association with live-birth rate and time to conception. Data confirm serum AMH levels improve menopause prediction, monitoring of ovarian damage, and identification of women at risk for several ovary-related disorders such as polycystic ovary syndrome and premature or primary ovarian insufficiency. However, it is now recognized that serum AMH results can have dramatic variability due to common, biologic fluctuations within some individuals, use of hormonal contraceptives or other medications, certain surgical procedures, specimen treatment, assay changes, and laboratory calibration differences. Practical guidelines are provided to minimize the impact of variability in AMH results and maximize the accuracy of clinical decision-making.

SUMMARY: AMH is an ovarian biomarker of central importance which improves the clinical management of women’s health. However, with the simultaneous rapid expansion of AMH clinical applications and recognition of variability in AMH results, consensus regarding the clinical cutpoints is increasingly difficult. Therefore, a careful approach to AMH measurement and interpretation in clinical care is essential.
Potential mechanisms for racial and ethnic differences in anti-Müllerian hormone and ovarian reserve.

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Abstract
Accumulating evidence suggests that reproductive potential and function may be different across racial and ethnic groups. Racial differences have been demonstrated in pubertal timing, infertility, outcomes after assisted reproductive technology (ART) treatment, and reproductive aging. Recently, racial differences have also been described in serum antimüllerian hormone (AMH), a sensitive biomarker of ovarian reserve, supporting the notion that ovarian reserve differs between racial/ethnic groups. The existence of such racial/ethnic differences in ovarian reserve, as reflected by AMH, may have important clinical implications for reproductive endocrinologists. However, the mechanisms which may underlie such racial differences in ovarian reserve are unclear. Various genetic factors and environmental factors such as obesity, smoking, and vitamin D deficiency which have been shown to correlate with serum AMH levels and also display significant racial/ethnic variations are discussed in this review. Improving our understanding of racial differences in ovarian reserve and their underlying causes may be essential for infertility treatment in minority women and lead to better reproductive planning, improved treatment outcomes, and timely interventions which may prolong reproductive lifespan in these women.