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★ Abstract title:

Fully automated assay assessment of intra- and inter-cycle variation for Anti-Müllerian hormone during the natural cycle

L. Melado Vidales¹, B. Lawrenz¹, J. Sibal², E. Abu², A. Navarro³, H. Mousavi Fatemi¹.

¹VI Middle East Fertility Clinic, Medical department, Abu Dhabi, United Arab Emirates.

²VI Middle East Fertility Clinic, Laboratory department, Abu Dhabi, United Arab Emirates.

³VI Foundation., Statistical Department, Valencia, Spain.

Study question:

Does Anti-Müllerian Hormone (AMH) have important intra- and inter-cyclic variations during the natural cycle when a fully automated assay is used for the sample analysis?

Summary answer:

With the use of a fully automated assay, AMH shows significant intra- and intercycle variations during the natural cycle, not caused by analytical variability.

What is known already:

AMH has emerged as one important clinical marker for ovarian reserve. Fully automated assays reduce analytical variability and enables more accurate evaluation of biological variations. The hormone shows strong correlation to the number of antral follicles and provides an important baseline assessment for individualizing of the therapeutic strategy in assisted reproductive techniques (ART). AMH has been considered a reliable test to be measured any day of the cycle without substantial variation. However, recent data have pointed towards important inter- and intra-cycle fluctuations and questioned whether a single AMH measurement is sufficient for decision-making in ART.

Study design, size, duration:

Prospective study including 22 volunteers from April to December 2017. Blood samples for AMH, FSH, LH, estradiol, and progesterone were obtained by venous puncture during the natural cycle on day 2/3, day 10, day of LH surge (LH surge was defined as LH concentration rise by 180% above the latest serum value), luteal phase (confirmed by elevated progesterone levels 8 days after LH surge), and day 2/3 of the subsequent bleeding.

Participants/materials, setting, methods:

Healthy volunteers between 18-37 years of age were included, with regular menstrual cycles and a BMI between 18-28 kg/m². Exclusion criteria: Intake of hormonal contraceptives for two previous months, pregnancy, breastfeeding, previous conditions with possible impact on the ovarian reserve (ovarian surgery, chemotherapy, radiation of the pelvis, ...). Blood for AMH-evaluation was stored at -20°C. For batch analysis, two kits of Elecsys® AMH automated (Roche for Cobas 601 platform®) were used.

Main results and the role of chance:

A total of 99 samples from 22 women with a median age of 30,7±4,11 years and a BMI of 23,2±3,63 were analysed. A substantial longitudinal fluctuation in AMH levels was found, expressed as coefficient of variation (CV) intra-cycle of 0,207, calculated for all individual readings per cycle day. Clinically, AMH value varied 20,7% throughout the cycle from the first serum analysis obtained at the beginning of the cycle with no clear pattern of fluctuation. Serum AMH levels were significantly altered by BMI and age (p<0,001), both negative correlated with AMH values. A positive correlation between LH and AMH concentrations was found (p=0,01), but not to other hormones. Absolute intra-individual inter-cyclic variability of AMH (cycleday 2-3 in two consecutive cycles) was 0,75 ng/mL (range: 0,03ng/mL - 2,81ng/mL) and inter-cycle CV was 0,28 (Confidence interval: 0,16-0,39; p<0,0001). No differences were found comparing variability of AMH between the assays used. The observed AMH fluctuations across the cycle are noticeably higher than expected from the assay imprecision and therefore seem more likely to

be caused by biologic variability.

Limitations, reasons for caution:

This study reports limited number of study subjects. However, an average of 4.5 blood-samples study subject were assayed in one run, eliminating inter/intra-assay bias in the normal cyclic women included. Further studies will have to investigate, whether AMH-fluctuations are also present in other subgroups of population.

Wider implications of the findings:

The large intercycle and intracycle AMH fluctuations in the same woman during her natural cycle using an automated assay keeps the question open on the best time to measure AMH for decision-making in daily practice. Further RCTs evaluating AMH dynamics and its correlation with treatment outcomes should be conducted.

Trial registration number:

This trial has been registered for [clinical.trials.gov](https://clinicaltrials.gov): NCT03106272.

Keywords:

Anti-Müllerian Hormone
natural cycle
intra-cycle variations
inter-cycle variations
fully automated assay