UNIVERSITY OF COPENHAGEN

FACULTY OF HEALTH AND MEDICAL SCIENCES

PhD Thesis

The clinical use of anti-Müllerian hormone in female reproduction

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English summary

The overall aim of this thesis was to gain knowledge on how to interpret serum AMH measurements in the context of female reproduction and to explore different uses. The results from one literature review and two clinical observational studies form the basis of this thesis.

Reviewing the literature, the current body of knowledge support the use of serum AMH measurements to improve female reproductive health. AMH has proven to be the most reliable and stable endocrine marker of ovarian reserve with a wide range of applications. Most notably, AMH measurements facilitate pretreatment counseling before initiating IVF. However, serum AMH has not proven to be a good predictor of live birth and furthermore, assay variability and the lack of an international standard for AMH immunoassays limits the ability to establish universally applicable cut-off values.

Study I was a prospective observational study of 64 women treated with salpingectomy for a tubal pregnancy with the aim to assess if salpingectomy affected the ovarian reserve measured by serum AMH levels. We found no reduction in AMH following salpingectomy. The intra-individual biological variation for AMH was calculated and ranged between 12.1% and 26.3%, depending on time between the two samples.

Study II was a prospective observational study of 107 women with limited ovarian reserve (AMH $\leq$ 12 pmol/L) undergoing one cycle of a fixed dose of maximal ovarian stimulation in the short GnRH-protocol. Serum AMH was measured before treatment start and at four time-points during one cycle. The ability of AMH to predict follicular development and ovarian response along with the changes in serum AMH during the cycle were assessed. We found that pre-treatment serum AMH levels significantly predicted inadequate follicular development, but AMH was not suitable for withholding fertility treatment, as even very low levels were associated with live births. During the stimulated cycle, AMH levels gradually declined, which correlated with the follicular recruitment. We propose that following maximal gonadotrophin stimulation for ART, the residual AMH in serum of approximately 40% originate from very small antral or even pre-antral follicles below the detection limit of ultrasound.

Dansk resumé

Det overordnede formål med denne ph.d.-afhandling var at opnå større viden omkring fortolkning af anti-Müllersk hormon (AMH) målinger i serum og at undersøge anvendelsen i klinisk praksis. Afhandlingen bygger på en litteraturgennemgang og to kliniske studier.

Litteraturgennemgangen understøtter brugen af serum AMH-målinger inden for reproduktiv sundhed hos kvinder. AMH har vist sig at være den mest pålidelige biokemiske markør for ægreserven og anvendes i vid udstrækning. Den bedst underbyggede indikation for AMH-målinger er inden påbegyndelse af fertilitetsbehandling, hvor AMH kan understøtte vejledning af patienter og optimering af behandling. Brugen af AMH-målinger er dog udfordret af analysevariation, da der endnu ikke findes en international standard for AMH immunanalyser. Derudover prædikterer AMH-målinger respons på gonadotropinstimulation snarere end graviditetschance.

Studie A var et prospektivt observationelt studie af 64 kvinder, som fik målt AMH før og efter de blev opereret for en tubar graviditet, med det formål at undersøge om operationen (salpingektomi) kunne have en negativ indflydelse på ægreserven. Vi fandt, at AMH ikke faldt efter operationen som udtryk for, at salpingektomi ikke har en umiddelbar indflydelse på ægreserven. Derudover fandt vi en relativ lav biologisk variation mellem AMH-målinger hos samme person over 3-6 måneder.

Studie B var et prospektivt observationelt studie af 107 kvinder med nedsat ægreserve (serum AMH ≤ 12 pmol/L), der blev fulgt gennem en stimulationscyklus i forbindelse med assisteret befrugtning. AMH blev målt inden behandlingsstart og fire gange under behandlingen. Resultaterne blev inddelt i to understudier. I studie B1 undersøgte vi, om AMH inden behandlingsstart kunne identificere de kvinder med så lav ægreserve, at assisteret befrugtning med egne æg ville være formålsløs, og som derfor må tilbydes ægdonation fra starten. Vi fandt, at AMH var en god, men ikke absolut prædiktor af dårligt respons på gonadotropin stimulation, da også kvinder med meget lav AMH blev gravide. I studie B2 fandt vi, at AMH i serum faldt i løbet af stimulationsbehandlingen, og at dette fald korrelerede til follikeludvikling. AMH-niveauet i serum kunne dog ikke udelukkende forklares ud fra antallet af antrale follikler, og resultaterne tyder på, at op imod 40% af AMH i serum stammer fra meget små antrale eller præantrale follikler, der endnu ikke er synlige på ultralydsskanning.