Session II: Measurement of Ovarian Reserve

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The Emerging Role of AMH as an Index of the Ovarian Reserve Across the Female Reproductive Lifespan.

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The basis for the value of AMH as a biomarker is that granulosa cells start producing AMH as soon as follicle growth is initiated, and that expression rapidly declines in antral follicles at approximately 8 mm diameter. This means that serum AMH concentrations are distinct from periovulatory events, although it is the smaller antral follicles rather than the preantral follicles that contribute the bulk of circulating concentrations. The field is hampered by the absence of an international standard against which assays can be calibrated but It has become clear that AMH predicts the ovarian response in IVF (the 'functional' ovarian reserve) and also reflects the size of the histologically determined primordial follicle count in humans as well as rodents (the 'true' ovarian reserve). AMH declines during the later reproductive years, with emerging data investigating the potential for prediction of the menopause. It also appears to reflect increasing ovarian activity in childhood. A small decline at pubertal onset has been confirmed in longitudinal studies, before a secondary rise to a peak in the mid 20s. This changing pattern in AMH concentration can be mapped against the rate at which follicles are lost from the histologically-determined non-growing pool, showing closely associated rises during childhood. This finding is consistent with the idea that most follicles leaving the non-growing pool start growing rather than becoming atretic directly. **CONCLUSION. Recent years have seen rapid emergence of the value of AMH in a number of different clinical contexts. It promises to be of further value in our understanding of ovarian development during childhood and puberty, and of the relationship between the rate of follicle loss and time to the menopause. In addition to being a valuable biomarker in observational studies this will lead to new experimental approaches advancing our understanding of follicle dynamics across the lifespan.**

Biomarkers of Ovarian Aging as Predictors of Fertility

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As the ovary ages, the granulosa cell products antimullerian hormone (AMH) and inhibin, decline leading to a rise in early follicular phase follicle stimulating hormone (FSH) and subsequent shortening of the follicular phase and menstrual cycle length. These biomarkers of ovarian aging-chronologic age, menstrual cycle length, serum or urinary early follicular FSH, and AMH- have been proposed as potential measures of female fertility. Chronologic age has been the most commonly used biomarker to predict fertility following assisted reproductive technology (ART) and natural fertility. Menstrual cycle length also appears to be associated with fecundability in assisted and unassisted attempts to conceive. However, the value of menstrual cycle length as a predictor is limited by the low prevalence of short menstrual cycles, oral contraceptive use, and menstrual cycle irregularity. While FSH has been shown to be a predictor of assisted fertility, it appears to have low sensitivity for non-pregnancy and has unproven value as a predictor of unassisted fertility. AMH appears to have the most promise. Serum levels of AMH have been shown to be directly associated with the probability of conceiving following ART and naturally; however, there are no studies to date that examine AMH test characteristics, e.g. sensitivity, specificity, in the prediction of natural fertility and infertility. **CONCLUSION: While historical and laboratory biomarkers of ovarian aging are associated with assisted and unassisted fertility, their value as predictors are unproven. These biomarkers require further study as "fertility tests" in the general population.**

Genetic Factors Influencing the Timing of Natural Menopause

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Understanding the genetic determinants influencing the timing of natural menopause may provide insights into normal reproductive function and clarify the biologic mechanisms underlying the association between menopause and key health conditions (e.g. cardiovascular disease, cancer, and osteoporosis). Heritability studies demonstrate that about 50 % of the variation in age at natural menopause is due to genetic factors. Candidate gene studies of menopause age have largely yielded inconsistent results in part due to small samples and lack of replication. Large genome-wide association studies conducted in women of European ancestry have successfully identified 17 genetic loci associated with age at menopause including genes implicated in hormone regulation, DNA repair, and immune function. At least two genes, *POLG* and *TDRD3*, may be associated with primary ovarian insufficiency. Many of the identified variants for normal menopause are also associated with early menopause suggesting some shared genetic factors. Initial