The *FMRI* gene in human reproduction

Aya-Shohat-Tal, PhD, Postdoctoral Associate, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT; Assistant Visiting Scientist, The Center for Human Reproduction, New York, N.Y.

Tandem CGG-repeat premutations and polymorphisms in the *FMR1* (fragile-X mental retardation 1) gene have been implicated in various forms of ovarian dysfunction, including premature ovarian failure (POF) and diminished ovarian reserve (DOR). Molecular studies suggest the FMR1 protein (FMRP) plays a role in folliculogenesis and inhibition of primordial follicle recruitment, resembling the role of anti-Mullerian hormone (AMH) in the ovary. Accordingly, research has focused on investigating the relationship between the rate of decline of AMH (a sensitive ovarian reserve marker) in carriers of different *FMR1* repeat alleles. Results from such studies will be systematically analyzed and their design-specific limitations discussed. Additionally, a molecular model for the interplay between FMRP and AMH will be proposed. A principal, unrepudiated conclusion emerging from the critical review is that in women with infertility and in fertile women with early ovarian decline, *FMR1* genotype is associated with the dynamics of AMH decline when subjects are stratified for age and/or CGG count. Longitudinal studies corroborating this finding are underway, as well as studies evaluating *FMR1* genotyping as a diagnostic tool for predicting diminishing ovarian reserve before the onset of AMH decline, which may allow women more informed reproductive planning and evaluation of fertility preservation options.

The potential diagnostic importance of conversion dynamics of DHEA to testosterone

Aya-Shohat-Tal, PhD, Postdoctoral Associate, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT; Assistant Visiting Scientist, The Center for Human Reproduction, New York, N.Y. 10021

Though the androgen precursor dehydroepiandrosterone (DHEA) is increasingly utilized to supplement IVF protocols in women with diminished ovarian reserve, disagreement still exists among some regarding its effectiveness. Failure to account for basal and post-treatment androgen levels may underlie discrepant findings, as the majority of studies examining the hormone's efficacy did not investigate patients' androgenic status prior to DHEA treatment nor response to DHEA treatment in terms of androgen elevation. Our group first demonstrated that women with diminished ovarian reserve who are also hypoandrogenic benefit most (in terms of improved IVF outcome) from DHEA treatment if their androgen levels significantly increase, as compared to women who are not hypoandrogenic or that are hypoandrogenic but their serum androgen levels fail to significantly increase following DHEA supplementation. Other than age-related decline in steroidogenic capacity, genetic differences in androgen metabolism may underlie this apparent failure to normalize androgen levels following treatment. Genetic variations may manifest molecularly as altered expression or altered enzymatic function of steroidogenic proteins involved in the conversion of DHEA to testosterone, or

their upstream regulators. Polymorphisms and mutations in genes involved in the conversion of DHEA to testosterone or their receptors will be discussed, as well as the mechanism by which they may affect female hormonal profiles. These include DHEA sulphotransferase, aromatase, steroid 5α-reductase, androgen receptor, sex-hormone binding globulin, fragile X mental retardation protein and breast cancer type 1 susceptibility protein. The diagnostic value of screening for these genetic markers will be discussed, as well as the potential for individualized fertility treatments alternative to DHEA for hypoandrogenic women with diminished ovarian reserve.