Genetic Predictors of ovulation induction regimes: Where we are today?

Dimitris Loutradis

1st Department of OB/GYN Athens Medical School. Division of Human Reproduction.

Investigators have focused on identifying a genetic tool that could predict the response to gonadotropin stimulation, by implementation of a patient’s genetic profile in the process of ovulation induction.

In this context, several genes have been studied, including those of the molecules involved in the estrogen pathway and the follicle-stimulating hormone (FSH) receptor LHR, AMH receptor.

Many polymorphisms of the FSH receptor gene have been discovered, but the most studied are the Ser680Asn and Thr307Ala ones. The Ser680Asn polymorphism of the FSH receptor gene has been found to influence the ovarian response to FSH stimulation in women undergoing IVF, as the FSH receptor in women carrying the Ser/Ser genotype appeared to be more resistant to FSH action. The clinical implications of this finding are highly important and the ultimate goal is the application of genetic markers as routine diagnostic tests before ovarian stimulation in order to predict the ovarian response, determine the required FSH dose and avoid the possible complications related to FSH stimulation.

We have examined the frequency distribution of the Ser680Asn polymorphism of the FSHR, in ovarian dysfunction (OD) infertile women, ‘poor responders’ (PR) and normo-ovulatory controls (good responders, GR) of Greek origin.

This study demonstrates that for OD patients the FSHR Ser/Ser variant was more prevalent (45.5%), while the Asn/Ser variant is correlated with more follicles and oocytes. Furthermore, data from the three different groups leads to the suggestion that the Ser/Ser variant is related with a higher level of serum FSH while the Asn/Ser variant with a lower. Furthermore, in the GR group, patients belong more often in the Asn/Ser genotype.

A hypothesis that a discrete set of genes including Greek population of women undergoing IVF/ICSI, alone and in combination, concerning the ovarian stimulation outcome and pregnancy rate. This study brings to light evidence that the patients carrying the polymorphisms in an homozygous state in both ESR1 and FSHR genes (simultaneously) are state in both ESR1 and FSHR genes (simultaneously) are over-presented in the poor responders group in a statistically significant way (p=0.038). This is supported also by the fact that this certain genotype combination presents the worst ovulation induction profile when compared with the rest of ovulation induction profile when compared with the rest of genotype combinations, considering the total amount of gonadotrophins used, the peak E2 and the number of follicles produced (p<0.05).

Luteinizing hormone (LH) exerts its actions through its receptor (LHR), which is mainly expressed in theca cells and to a lesser extent in oocytes, granulosa and cumulus cells. The aim of the present study was the investigation of a possible correlation between LHR gene and LHR splice variants expression in cumulus cells and ovarian response as well as ART outcome. Forty patients undergoing ICSI treatment for male factor infertility underwent a long luteal GnRH-agonist downregulation protocol with a fixed 5-day rLH pre- treatment prior to rFSH stimulation and samples of cumulus cells were collected on the day of egg collection. RNA extraction and cDNA preparation was followed by LHR gene expression investigation through real-time PCR. Cumulus
cells were investigated for the detection of LHR splice variants using reverse transcription PCR. Concerning LHR expression in cumulus cells, a statistically significant negative association was observed with the duration of ovarian stimulation (odds ratio 0.23, p < 0.012). Interestingly, 6 over 7 women who fell pregnant expressed at least two specific types of LHR splice variants (735 bp, 621 bp), while only 1 out of 19 women that did not express any splice variant achieved a pregnancy. However the present study provide a step towards a new role of LHR gene expression profiling as a biomarker in the prediction of ovarian response at least in terms of duration of stimulation and also a tentative role of LHR splice variants expression in the prediction of pregnancy success.

AMH (as a paracrine product of immature follicles) is a more direct measure of ovarian status compared with other endocrine reproductive hormones. AMH is primarily produced by the preantral and small antral follicles, and correlates with the number of primordial follicles at the gonadotrophin-independent stage of follicular development. The inhibitory action of AMH on the physiology of ovaries is due: a) to the initial recruitment of follicles independently of FSH b) to the cyclic recruitment: rescue of a restricted number of antral follicles from atresia. In the absence of AMH primordial follicles are recruited at a faster rate, resulting in premature exhaustion of the primordial follicle pool and consequently to a premature menopause. The first end point in our study was to examine the distribution of AMH and AMHRII SNPs in the Greek population and the second end point to investigate the possible association between the presence or not of polymorphisms and the different parameters of ovarian stimulation in women undergoing IVF. Women of IVF group heterozygotes or homozygotes for AMH polymorphism (Ile/Ser και Ser/Ser) showed statistically significant higher E2 values at ovulation compared to women without the polymorphism (Ile/Ile) (p-value = 0.009). Women of IVF group – carriers of AMHRII SNP (A/G και G/G) showed: statistically significant lower levels of E2 at ovulation (p-value = 0.009). Statistically significant lower number of follicles (p-value = 0.026). Statistically significant lower number of oocytes (p-value = 0.034). Our conclusions are: 1. AMH SNP and without AMHRII SNP probably have a better prognosis regarding the outcome of ovarian stimulation. 2. Women carriers of the AMHRII SNP perhaps should be treated as “poor responders” modification of gonadotrophin dose according to the genetic profile of each patient.

In conclusion the impact of these factors (Genetics) may be small. In order to ensure that a beneficial effect is achieved, an array of molecular tools will be needed and hundreds of thousands of polymorphisms must be examined in appropriate phenotypic groups such as “poor responder” patients. Genotyping of patients scheduled for ovarian stimulation could be an attractive tool to individualize FSH dosage according to the genetic differences in ovarian sensitivity.