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ESR1 and ESR2 gene polymorphisms are associated with human reproduction outcomes in Brazilian women

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Abstract

Background: Important candidate genes involved in the ovarian response to exogenous FSH are the estrogen receptor genes (ESRs), since the effects of estrogens on follicle growth, maturation and oocyte release. It is known that some markers of ovarian stimulation can help to personalize the treatment, adjusting the dose of exogenous rFSH, thus preventing excessive wear of the patient. Inspired on this information we aimed to analyze four different polymorphisms in the estrogen receptor genes *ESR1*: rs2234693/T-397C (*PvuII*) and rs9340799/A-351G (*XbaI*) and *ESR2*: rs4986938/G1082A (*RsaI*) and rs1256049/A + 1730G (*AluI*), and their association with assisted reproduction outcomes in Brazilian women that underwent *in vitro* fertilization (IVF).

Methods: A cross-sectional study was performed involving 136 infertile women less than 39 years of age with normal ovarian reserve. Patients were divided according to the same COH protocol for statistical analysis. The Taqman assay was used for *PvuII* and *XbaI* of *ESR1*, and *RsaI* and *AluI* of *ESR2* genotyping. Serum estradiol and FSH were measured by Elisa assay.

Results: The *PvuII* (*ESR1*) TT and *RsaI* (*ESR2*) GG genotypes were associated with a longer induction period and higher doses of medication ($p < 0.03$). The *XbaI* (*ESR1*) AA genotype was associated with better COH results, including a larger number of follicles, mature oocytes, embryos, and good quality embryos ($p < 0.05$). The *AluI* GG genotype showed an association with the Ovarian Hyperstimulation Syndrome (OHSS) ($p = 0.03$). According to the haplotype analysis of *ER1* (*PvuII/XbaI*), we demonstrated that the CA combination increases by 0.68 the number of good quality embryos while the TG decreases it by 0.71 ($p = 0.04$).

Conclusion: ER polymorphisms have an association with the assisted reproduction outcomes in Brazilian women.

Keywords: Estrogen receptor gene, Polymorphism, *In vitro* fertilization, Controlled ovarian hyperstimulation

Introduction

Infertility is a health problem that affects 15–20% of couples at a reproductive age [1], with several medical, emotional, and social implications. The use of *in vitro* fertilization (IVF) has improved the treatment prospects for infertility by diverse causes. In developed countries, it is estimated that 2–3% of all births are results of IVF procedures [2].

IVF is a multistep process that still has limited successful rates regardless of constant improvement in laboratory performance, as it also depends on interindividual variability factors such as ovarian response after controlled ovarian hyperstimulation (COH). Both quantitative and qualitative factors in oocyte production have a high influence on the IVF outcome, since increasing the number of mature oocytes improves the selection of viable embryos for transfer [3].

Although low response rates can lead to cycle cancellation, high responses are troublesome as they can trigger a serious medical iatrogenic condition – the ovarian hyperstimulation syndrome (OHSS). This unpredictable

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