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GONADOTROPHIN RECEPTOR POLYMORPHISMS (FSHR N680S AND LHCGR N312S) ARE NOT PREDICTIVE OF CLINICAL OUTCOME AND LIVE BIRTH IN IVF CYCLES.

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OBJECTIVE: Recent studies reported that women with homozygous alleles for serine (S) in both FSHR (rs 6166) and LHCGR (rs 2293275) polymorphisms had a 40% higher chance of live birth compared to those with other genotypes after in vitro fertilization (IVF) cycle. Given the major repercussions that these findings might bring to clinical practice, this study aimed to investigate any association between different polymorphism combinations of both FSHR and LHCGR and clinical outcomes in IVF cycles with preimplantation genetic testing for aneuploidy (PGT-A), therefore controlling for the embryo ploidy status.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All women age 18-40 undergoing their first IVF cycle with aneuploidy screening between 2006-2017 with body mass index <40 were included. All patients received both recombinant FSH and hMG. GenomicDNAwas isolated from patient's blood. For the genotyping of the aforementioned variants, allelic discrimination for the FSHR and LHCGR receptor polymorphisms were performed using TaqMan genotyping assays. Associations between both receptor genotypes and clinical TABLE 1. Clinical outcomes for different polymorphism combinations of both FSHR and LHCGR.

FSH/LH Number of patients: 1183 Oocyte yield Mean MII rate Usable Blastocyst rate Succesfull discharge Implantation rate Live birth NN:NN 44 17.36 +/- 10.03 76.4%(73.3-79.4) 40.6%(36.6-44.7) 59.1%(43.2-73.7) 53.4%(39.9-66.7) 56.8%(41.0-71.7) NN:NS 169 17.33 +/- 9.79 77.4% (75.8-78.9) 44.5%(42.5-46.6) 70.4%(62.9-77.2) 60.1%(53.3-66.6) 68.0%(60.4-75.0) NN:SS 132 17.61 +/- 10.57 79.1% (77.4-80.7) 46.2%(43.9-48.5) 71.2%(62.7-78.8) 63.6% (55.9-70.8) 69.7%(61.1-77.4) NS:NN 93 16.97 +/- 10.96 73.1% (70.9-75.3) 42.7%(39.9-45.6) 62.4%(51.7-72.2) 57.6%(48.2-66.7) 60.2%(49.5-70.2) NS:NS 258 17.10 +/- 10.75 74.5%(73.2-75.8) 44.9%(43.2-46.6) 65.9%(59.8-71.7) 60.8%(55.3-66.0) 62.8%(56.6-68.7) NS:SS 230 16.54 +/- 10.63 75.4% (74.0-76.8) 42.8%(41.0-44.6) 67.8%(61.4-73.8) 61.6%(55.8-67.1) 64.8%(58.2-70.9) SS:NN 47 17.21 +/- 10.84 73.3% (70.1-76.3) 42.1%(38.1-46.1) 70.2%(55.1-82.7) 65.1%(52.0-76.7) 68.1%(52.9-80.9) SS:NS 116 17.33 +/- 11.06 73.0% (71.0-75.0) 43.8%(41.2-46.3) 64.7%(55.2-73.3) 64.4%(56.2-72.1) 64.7%(55.2-73.3) SS:SS 94 17.29 +/- 12.47 77.1%(75.0-79.1) 42.1%(39.3-44.8) 53.2%(42.6-63.6) 50.4%(41.1-59.7) 51.1%(40.5-61.5) P value 0.2082 2.07x10-6 0.118 0.234 0.344 0.237 FERTILITY & STERILITY_ e59 outcomes was assessed using generalized regression and ANOVA. Live birth rate was the primary outcome. Secondary outcomes included: oocyte yield, mature oocytes (MII) rate, blastocyst rate, usable blastocyst rate, and implantation rate.

RESULTS: 1183 patients met the inclusion criteria and generated reliable genotype calls. The overall genotype frequencies in the study population for the FSHR gene were: 21.7% homozygous for S in codon 680, 29.2% homozygous for N680 and 48.1% heterozygous

(N680S). As for the LHCGR, 15.6% were homozygous for N312, 45.9% heterozygous (N312S) and 38.5% homozygous for S312. Our study population consisted of 53.8% white non-Hispanic, 6.1% white Hispanic, 4.1% Afro-American, 15.4% Asian, 20.6% other or unknown. No significant association was found with any of the studied variables (oocyte yield,usable blastocyst rate,implantation rate,- live birth) when genotypes were analysed per receptor or in combination with one another (Table 1). There was a statistically significant but clinically insignificant difference in the rate of MIIs across different variants combinations.

CONCLUSIONS: Our findings suggest that the presence of gonadotrophin receptor polymorphisms is not associated with assisted reproductive technique (ART) outcomes, therefore these variants should not be considered as reproductive predictors. References: 1. Lindgren I, Giwercman A, Axelsson J, Lundberg Giwercman Y. Association between follicle-stimulating hormone receptor polymorphisms and reproductive parameters in young men from the general population. Pharmacogenet Genomics 2012;22:667-72. 2. Kuijper EA, Blankenstein MA, Luttikhof LJ, Roek SJ, Overbeek A, Hompes PG et al. Frequency distribution of polymorphisms in the FSH receptor gene in infertility patients of different ethnicity. Reprod Biomed Online 2010;20:588-93. 3. Valkenburg O, Uitterlinden AG, Piersma D, Hofman A, Themmen AP, de Jong FH et al. Genetic polymorphisms of GnRH and gonadotrophic hormone receptors affect the phenotype of polycystic ovary syndrome. Human reproduction (Oxford, England) 2009;24:2014-22. 5. Lindgren I, Baath M, Uvebrant K, Dejmek A, Kjaer L, Henic E, et al. Combined assessment of polymorphisms in the LHCGR and FSHR genes predict chance of pregnancy after in vitro fertilization. Human reproduction (Oxford, England) 2016;31:672-83. Supported by: Foundation of Embryonic Competence.