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CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-OH DEFICIENCY CARRIER STATUS IS NOT ASSOCIATED WITH IMPAIRED OOCYTE OR EMBRYONIC QUALITY

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OBJECTIVE: Limited research has been published about infertility and patients who are heterozygous carriers for Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-OH CAH). Some studies have shown that 21-OH CAH carriers experience some degree of hormonal disturbances, especially in androgen biosynthesis [1,2]. Our study aims to evaluate whether 21-OH CAH carriers who undergo IVF are at a greater risk of having suboptimal ovarian stimulation and IVF outcomes as compared with the general infertile population.

MATERIALS AND METHODS:
Patients at a single center who underwent their first IVF treatment from 2018 to 2021 were analyzed. PGT-A with NGS was performed for all cases. All couples underwent preconception expanded carrier screening. Patients were segregated into groups based on female *CYP21A12* carrier status: heterozygote carriers for 21-OH CAH; and patients who were not found to carry any pathogenic variants in *CYP21A2*. Patients with biallelic *CYP21A2* mutations were excluded. Baseline characteristics, ovarian stimulation parameters, oocyte quality, blastulation and embryo ploidy rates were compared. Comparative statistics and an adjusted regression analysis was performed. A sample size of 121 patients per cohort was calculated to ensure an 80% power to detect a difference of 15% on euploidy rates (α=0.05).

RESULTS: 2,587 cycles were included. A 7.65% 21-OH CAH Carrier status prevalence was observed. 22 different pathogenic variants in CYP21A2 were identified being c.841G>T, p. V281L (60.6%) the most common. 198 carriers were compared with 2,389 non-carrier controls. No differences in age, BMI, AMH, AFC, FSH, DHEAS and testosterone levels were observed among cohorts. A significant difference was found in progesterone level at surge (A=1.01±0.6 vs B=1.1±0.5, p=0.01) and 17 OH progesterone levels (67.0±73.9 vs 226.5±322.1, p=<0.0001), but no differences were found in days of stimulation, gonadotropin dose and oocytes. Furthermore, maturity rates, fertilization, blastulation, and euploidy rates were comparable between the two groups. In a multivariate analysis adjusted for age, BMI, AMH, year of treatment and ethnicity, no association was found with between 21-OH CAH carrier status and lower oocyte maturity (OR 1.11 CI95% 0.5-2.3); lower fertilization (OR 1.63, 0.7-3.4); lower blastulation (OR 1.04, 0.4-2.2); or lower euploidy rates (OR 1.7, 0.8-3.8). Finally, the type of 21-OH CAH gene variant (classic vs non-classic) was not associated with lower oocyte maturity, fertilization, blastulation and euploidy rates.

CONCLUSIONS: It has been suggested that 21-OH CAH carriers might experience some degree of disruption in 21-hydroxylase enzymatic activity, raising the question of potential impact on fertility treatment outcomes. Our study shows that 21-OHCAH carriers have similar ovarian stimulation outcomes as the general infertile population.

IMPACT STATEMENT: Given how common carrier frequency is for this mutations in the general population, many patients can now be reassured their chances of producing good quality oocytes and obtaining euploid embryos are similar to non-carriers.

REFERENCES:

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