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Title:

CYSTIC FIBROSIS HETEROZYGOSITY DOES NOT IMPACT OVARIAN RESERVE OR ASSISTED REPRODUCTIVE TECHNOLOGY OUTCOMES

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Background:

Cystic fibrosis (CF) carrier status has been hypothesized to modulate female reproductive function, as the CFTR gene has been observed to be in the proximity of several fertility and primary ovarian insufficiency-related genes on chromosome 7 [1]. In mouse-model studies, the CFTR gene has been identified to control HCO3 entry into ovarian and granulosa cells, which consecutively regulates FSH-stimulated estrogen [2] and influences follicular fluid accumulation during oocyte maturation [3]. Previous published research has shown that CFTR mutation heterozygosity does not impact ovarian response and IVF cycle outcome [4], albeit this study was performed prior to the current era of routine preimplantation genetic testing (PGT).

Objective:

The objective of this study was to comprehensively evaluate ovarian reserve and ART treatment outcomes in female CF carriers.

Materials and Methods:

Patients who underwent expanded carrier screening and IVF (with or without PGT) from June 2012 to March 2018 were included in the retrospective, cohort study. The study included heterozygote CF carriers and controls that tested negative (non-carriers) for all mutations. Baseline demographics, ovarian reserve, IVF laboratory outcomes, embryonic aneuploidy and embryo transfer outcomes were compared between CF carriers and controls. A sub-analysis restricted to patients undergoing single, euploid FETs was conducted to assess the effect of CFTR mutation heterozygosity on embryo transfer outcome. Student's t-test, chi-square test, and multivariate linear and binary logistic regression models were used for data analysis. A mixed model was used to account for patients that underwent multiple cycles.

Results:

CF carriers (n=135) were compared to non-carriers (n=1214). Baseline demographic factors, ovarian reserve, cycle IVF cycle characteristics, embryonic aneuploidy screening results and embryo transfer outcome are shown in Table 1. When controlling for age, CF heterozygosity did not impact AMH (β=-0.34, p=0.45) or BAFC (β=-0.8, p=0.21). Controlling for age and AMH, CF carriers did not have altered oocyte yield (β=0.35, p=0.66), fertilization (β=-0.06, p=0.078), blastulation (β=-0.005, p=0.03) or embryonic aneuploidy (β=0.05, p=0.28). A sub-analysis restricted to patients undergoing single, euploid, FETs compared transfer outcome in heterozygous CF carriers (n=54) and non-carrier (n=437). Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy, CF heterozygosity did not impact the odds of implantation (OR 0.87 [95% CI 0.47-1.63], p=0.67), ongoing pregnancy (OR 0.84 [95% CI 0.46-1.55], p=0.58), early pregnancy loss (OR 1.25 [95% CI 0.56-2.78], p=0.59) or live birth (OR 0.95 [95% CI 0.43-2.10], p=0.89).

Conclusion:

As personalized medicine advances to include routine expanded carrier screening, it is now possible to evaluate specific genomic questions, such as whether CFTR mutation is a genetic determinant of female infertility. We demonstrated that women with single-allele CF mutations should not be concerned that their ovarian reserve, response, embryo quality, and overall treatment outcome will be negatively impacted. Female reproductive function and/or gametes do not appear vulnerable to a single allele mutation in the CFTR gene. Given the genotypic heterogeneity in CFTR mutations, further research is needed to elucidate whether specific mutations and variants confer differential risks to female reproductive health.

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Table 1:

	CF Carriers	Controls	p value
Patients	135	1214	
Oocyte age	36.3 ± 4.4	36.1 ± 4.8	0.6685
BMI (m^2)	23.2 ± 11.4	23.7 ± 4.2	0.2013
AMH (ng/ml)	3.6 ± 6.5	3.4 ± 4.1	0.701
BAFC	11.4 ± 7.5	10.6 ± 6.4	0.3783
IVF cycles	126	945	
Patients undergoing IVF	74	586	
Mature oocytes retrieved	13.3 ± 7.8 (1267)	12.7 ± 9.0 (8828)	0.5415
Fertilization Rate	68.0% (861/1267)	72.3% (6381/8828)	0.001
Day 3 embryos	7.5 ± 5.7 (835)	7.3 6.1 (6116)	0.6931
Day 5 embryos	5.1 ± 4.7 (569)	4.8 4.7 (4071)	0.5584
Blastulation rate	66.1% (569/861)	63.8% (4071/6381)	0.1892
Embryos biopsied for PGT	4.8 ± 4.0 (372)	4.1 3.6 (2361)	0.1389
Aneuploidy Rate	42.7% (159/372)	45.6% (1077/2361)	0.30
Single euploid FET cycles	54	437	
Implantation rate	63.0% (34/54)	58.8% (257/437)	0.56
Ongoing pregnancy rate	57.4% (31/54)	53.3% (233/437)	0.57
Early pregnancy loss rate	25.0% (10/40)	14.4% (45/313)	0.081
Live birth rate	43.3% (13/30)	41.3% (93/225)	0.83

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