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Title:

GAUCHER'S DISEASE CARRIERS DEMONSTRATE IMPROVED ART OUTCOME

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Objective:

Gaucher's disease is an autosomal recessive disorder of glycolipid storage, caused by a mutation in the gene that codes for the lysosomal enzyme, glucocerebrosidase (GBA). The accumulation of glucocerebrosides (GC) in macrophages lead to the multiorgan infiltration of GC laden lysomes, commonly referred to as "Gaucher cells." Homozygous affected females have been reported to have delayed menarche and puberty (Kaplan et al., 2006), impaired fertility, adverse pregnancy outcomes, and problems with lactation (Granovsky-Grisaru et al., 1995), suggesting that Gaucher cell infiltration affects the reproductive system. Furthermore, enzyme replacement therapy has been demonstrated to reduce the risk of early pregnancy loss in women with the full mutation (Zimran et al., 2009). There is a lack of data on the effect of GBA mutation heterozygosity on female reproductive health. The objective of our study was to examine the ovarian reserve and ART outcome of Gaucher's disease carriers.

Design:

Retrospective, cohort study

Materials and Methods:

Patients underwent expanded carrier screening from June 2012 to March 2018. The study included heterozygote GBA carriers and controls that tested negative for all mutations. Baseline demographics, ovarian reserve, IVF laboratory outcomes, embryonic aneuploidy and embryo

transfer outcomes were compared between GBA heterozygotes and controls. A subanalysis restricted to patients undergoing single, euploid FETs was conducted to assess the effect of GBA 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:

GBA mutation carriers (n=56) 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, GBA heterozygosity did not impact AMH (□=-0.9, p=0.19) or BAFC (□=-0.9, p=0.37). After controlling for age and AMH, GBA heterozygosity was associated with significantly increased oocyte yield (□=3.3, p=0.006). GBA mutation carriers had an overall lower fertilization rate, a greater mean number of day 3 and day 5 embryos cultured, a higher proportion of embryos that reached the blastocyst stage, and a lower proportion of biopsied embryos found to be aneuploid. However, controlling for age and AMH, GBA carrier status was not seen to impact fertilization (□=0.016, p=0.74), blastulation (□=-0.04, p=0.43) or embryonic aneuploidy (□=0.05, p=0.4). A subanalysis restricted to patients undergoing single, euploid, FETs compared transfer outcome in heterozygous GBA carriers (n=21) vs. controls (n=437). Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy, GBA heterozygosity did not significantly impact the odds of implantation (OR 0.8 [95% CI 0.32-2.06], p=0.64), ongoing pregnancy (OR 2.8 [95% CI 0.88-8.83], p=0.08), live birth (OR 0.66 [95% CI 0.21-2.11], p=0.49), or clinical pregnancy loss (OR 1.36 [95% CI 0.17-11.2], p=0.77).

Conclusion:

In the first study to investigate the impact of a single allele GBA mutation on female reproductive function, we demonstrated that Gaucher's disease carriers have similar ovarian reserve and embryo aneuploidy rates as compared to non-carriers. However, GBA carriers demonstrated more eggs in response to ovarian stimulation and more embryos available than non-carriers. This may prove to be an example of 'heterozygote advantage'- a phenomenon whereby a heterozygote genotype confers a higher relative fitness than the healthy, homozygote wild type (i.e. sickle cell trait individuals' resistance to malarial infection). The heterozygote advantage in GBA carriers is likely limited to folliculogenesis and oocyte and embryo development, as the presence of euploid embryos at transfer were shown to have similar odds of implantation and live birth as compared to non-carriers. Large scale studies are required to further elucidate the paradoxical relationship between GBA carrier status and ovarian response to COH.

Table 1:

	GBA Mutation Carriers	Controls	p value
Patients	56	1214	
Oocyte age	35.1 ± 5.6	36.1 ± 4.8	0.19
BMI	23.5 ± 4.8	23.7 ± 4.2	0.71
AMH	4.5 ± 7.6	3.4 ± 4.1	0.36
BAFC	11.9 ± 7.1	10.6 ± 6.4	0.23
IVF cycles	54	945	
Patients undergoing IVF	36	586	
Oocytes retrieved	17.1 ± 15.5 (937)	12.7 ± 9.0 (8828)	0.05
Fertilization Rate	60.3% (518/859)	72.3% (6381/8828)	<0.0001
Day 3 embryos	10.3 ± 9.8 (514)	7.3 ± 6.1 (6116)	0.04
Day 5 embryos	8.0 ± 8.6 (400)	4.8 ± 4.7 (4071)	0.01
Blastulation rate	77.2% (400/518)	63.8% (4071/6381)	<0.0001
Embryos biopsied for PGT	5.9 ± 4.5 (237)	4.1 ± 3.6 (2361)	0.02
Aneuploidy Rate	35.8% (85/237)	45.6% (1077/2361)	0.004
Single euploid FET cycles	21	437	
Implantation rate	66.7% (14/21)	58.8% (257/437)	0.47
Ongoing pregnancy rate	61.9% (13/21)	53.3% (233/437)	0.44
Clinical pregnancy loss rate	7.1% (1/14)	9.3% (24/257)	1.05
Live birth rate	53.8% (7/13)	41.3% (93/225)	0.37

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