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Title:

SMN1 HETEROZYGOSITY IS ASSOCIATED WITH DECREASED ANEUPLOIDY RATES

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Objective:

Spinal muscular atrophy (SMA), a neuromuscular disorder caused by biallelic mutations in the survival of motor neuron 1 (SMN1) gene, is characterized by loss of motor neurons, progressive muscle wasting, and often early death. Patients with neuromuscular disorders demonstrate impaired responsiveness to controlled ovarian hyperstimulation, perhaps related to impaired gonadal function[1]. In a mouse model, SMN1 mutation was associated with reduced testis size and impaired spermatogenesis, but no difference was shown in ovarian size or function[2]. Low SMN protein in mouse testes was associated with a number of changes including enrichment in genes that are highly active in somatic and early spermatogenic cell types, as well as upregulation in a number of pro-apoptotic proteins[2]. There is minimal data on the effect of SMN1 heterozygosity on human fertility treatment outcomes[1]. The objective of this study was to examine the ovarian reserve and ART outcomes of SMN1 mutation carriers.

Design:

Retrospective, cohort study

Materials and Methods:

The study included female patients who underwent expanded carrier screening and ART treatment from June 2012 to March 2018. The study compared heterozygote SMN1 carriers with controls that tested negative for all mutations. Baseline demographics, ovarian reserve, IVF laboratory outcomes, embryonic aneuploidy and embryo transfer outcomes were compared between SMN1 heterozygotes and controls. A sub-analysis restricted to patients undergoing single, euploid FETs was conducted to assess the effect of SMN1 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:

SMN1 mutation carriers (n=76) were compared to non-carriers (n=1214). Baseline demographic factors, ovarian reserve, IVF cycle characteristics, embryonic aneuploidy screening results and embryo transfer outcome are shown in Table 1. When controlling for age, SMN1 heterozygosity did not impact AMH (□=0.7, p=0.19) or BAFC (□=0.7, p=0.4). When controlling for age and AMH, SMN1 carrier status was not found to impact oocyte yield (□=-0.8, p=0.4), fertilization (□=0.01, p=0.74), or blastulation (□=0.03 p=0.4). In the same model, SMN1 carriers had a significantly lower degree of embryonic aneuploidy (□=-0.1, p=0.045). A subanalysis restricted to patients undergoing single, euploid FETs compared transfer outcome in heterozygous SMN1 carriers (n=28) vs. controls (n=437). When controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy; SMN1 heterozygosity did not significantly impact the odds of implantation (OR 0.93 [95% CI 0.45-1.92], p=0.9), ongoing pregnancy (OR 0.84 [95% CI 0.41-1.71], p=0.6), live birth (OR 0.91 [95% CI 0.38-2.17], p=0.8), or clinical pregnancy loss (OR 2.2 [95% CI 0.48-9.8], p=0.3).

Conclusion:

SMN1 carrier status was not associated with suboptimal ovarian reserve or oocyte yield. Single, euploid FET outcomes in SMN1 heterozygotes were similar to controls. Notably, there was a significant decrease in the rate of embryonic aneuploidy in SMN1 heterozygotes. If human gonads exhibit a similar response to low SMN protein found in mouse testes, with enrichment in early cell-line genes and upregulation of pro-apoptotic proteins[2], SMN1 mutation could protect against meiotic errors and prevent aneuploidy by eradicating abnormal oocytes. Female SMN1 heterozygotes should be reassured that fertility outcomes are not negatively impacted. Rather, patients with carrier status may experience a heterozygote advantage that reduces the rate of embryo aneuploidy. Further inquiry is needed into the mechanism behind the decreased rate of aneuploidy in this population.

Table 1:

	SMN1 Mutation Carriers (n=76)	Controls (n=1,214)	p value
Oocyte age	36.0 ± 4.7	36.1 ± 4.8	0.90
AMH	2.7 ± 2.4	3.4 ± 4.1	0.07
BAFC	9.8 ± 5.0	10.6 ± 6.4	0.31
Oocytes retrieved	12.9 ± 8.7 (746)	12.7 ± 9.0 (8828)	0.91
Fertilization Rate	72.4% (427/590)	72.3% (6381/8828)	0.96
Blastulation rate	62.3% (266/427)	63.8% (4071/6381)	0.53
Aneuploidy Rate	37.6% (76/202)	45.6% (1077/2361)	0.03
Implantation rate	53.6% (15/28)	58.8% (257/437)	0.59
Ongoing pregnancy rate	50.0% (14/28)	53.3% (233/437)	0.73
Clinical pregnancy loss rate	20.0% (3/15)	9.3% (24/257)	0.18
Live birth rate	39.2% (11/28)	41.3% (93/225)	0.84

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