American Society for Reproductive Medicine 2018 Scientific Congress & Expo
October 6 to 10, 2018 ● Denver, Colorado, USA

Title:

FEMALE REPRODUCTIVE FUNCTION IN WILSON'S DISEASE CARRIERS: OVARIAN RESERVE AND ART OUTCOME ARE NOT AFFECTED BY A SINGLE-ALLELE ATP7B MUTATION

Authors:

Sekhon L[1, 2], Luscher Z[2], Cacchione TA[1], Lee JA[1], Mukherjee T[1, 2], Copperman AB[1, 2]

Affiliations:

1. Reproductive Medicine Associates of New York, 635 Madison Ave 10th Floor New York, New York, United States, 10022
2. Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, Klingenstein Pavilion 1176 Fifth Avenue 9th Floor New York, New York, United States, 10029

Objective:

Wilson's disease is a rare disorder of copper metabolism caused by homozygous mutations in the ATPase Copper Transporting (ATP7B) gene. Multiple organs are affected by the oxidative damage that results from copper deposition. Copper deposits can even occur in the reproductive system, as evidenced by reports of amenorrhea and infertility in affected women (Tarnacka et al., 2000). Furthermore, a recent study from Japan measured serum copper levels in IVF patients undergoing frozen embryo transfer (FET) and reported an association between elevated serum copper levels and implantation failure (Matsubayashi et al., 2017). Individuals with single-allele ATP7B mutations have been shown to have modestly elevated urinary copper levels and are at an increased risk of depression and Parkinsonism (Pfeiffer et al., 2007). There is a lack of data on the effect of ATP7B mutation heterozygosity on female reproductive health. The objective of our study was to examine the ovarian reserve and clinical outcomes of Wilson's disease carriers in patients that underwent ART.

Design:

Retrospective, cohort study

Materials and Methods:

Between June 2012 and March 2018, patients underwent expanded carrier screening in preparation for ART cycles. The study included heterozygote ATP7B 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 ATP7B mutation heterozygotes and controls. A sub-analysis restricted to patients undergoing single, euploid FETs was conducted to assess the effect of ATP7B 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 undergoing multiple cycles.

Results:

ATP7B mutation carriers (n=48) 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, ATP7B heterozygosity did not impact AMH (□=1.05, p=0.1) or BAFC (□=0.07, p=0.9). Controlling for age and AMH, ATP7B carrier status was not seen to impact oocyte yield (□=-1.5, p=0.2), fertilization (□=0.02, p=0.6), blastulation (□=-0.02 p=0.74) or embryonic aneuploidy (□=-0.03, p=0.6). A subanalysis restricted to patients undergoing single, euploid, FETs compared transfer outcome in heterozygous ATP7B carriers (n=36) vs. controls (n=437). Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy, ATP7B heterozygosity did not significantly impact the odds of implantation (OR 1.2 [95% CI 0.53-2.94], p=0.6), ongoing pregnancy (OR 0.96 [95% CI 0.41-2.28], p=0.93), live birth (OR 1.5 [95% CI 0.47-4.59], p=0.5), or clinical pregnancy loss (OR 0.47 [95% CI 0.14-1.62], p=0.2).

Conclusion:

While there is evidence that a partial loss of ATP7B function can result in some degree of impaired copper metabolism leading to various clinical manifestations, our study is the first to evaluate whether ATP7B mutation heterozygosity impacts ovarian reserve and reproductive outcome. Our findings suggest that despite reduced ATP7B function, carriers of Wilson's disease have ART outcome comparable to that of non-carriers. It is possible that the modest reduction in copper metabolizing ability in carriers does not meet the threshold required to affect hypothalamic-pituitary-ovarian function or the environment surrounding embryo implantation. Further research is required to confirm these findings in a non-ART population, and to investigate whether there are copper level thresholds beyond which reproductive function is affected.

Table 1:

	ATP7B Mutation Carriers	Controls	p value
Patients	48	1214	
Oocyte age	36.6 ± 4.9	36.1 ± 4.8	0.58
BMI	23.5 ± 3.8	23.7 ± 4.2	0.71
AMH	2.2 ± 2.4	3.4 ± 4.1	0.02
BAFC	10.4 ± 4.5	10.6 ± 6.4	0.82
IVF cycles	45	945	
Patients undergoing IVF	23	586	
Oocytes retrieved	14.8 ± 6.8 (649)	12.7 ± 9.0 (8828)	0.07
Fertilization Rate	76.8% (361/470)	72.3% (6381/8828)	0.03
Day 3 embryos	8.0 ± 5.0 (352)	7.3 ± 6.1 (6116)	0.44
Day 5 embryos	4.7 ± 3.5(206)	4.8 ± 4.7 (4071)	0.77
Blastulation rate	57.1% (206/361)	63.8% (4071/6381)	0.01
Embryos biopsied for PGT	4.0 ± 2.3 (139)	4.1 ± 3.6 (2361)	0.74
Aneuploidy Rate	55.4% (77/139)	45.6% (1077/2361)	0.02
Single euploid FET cycles	36	437	
Implantation rate	47.2% (17/36)	58.8% (257/437)	0.18
Ongoing pregnancy rate	41.6% (15/36)	53.3% (233/437)	0.18
Clinical pregnancy loss rate	11.8% (2/17)	9.3% (24/257)	0.95
Live birth rate	30.4% (7/23)	41.3% (93/225)	0.31

References:

1. Tarnacka B, Rodo M, Cichy S, Czlonkowska A. Procreation ability in Wilson's disease. Acta Neuroloica Scandinavica 2000; 101: 395-398.
2. Matsubayashi H, Kitaya K, Yamaguchi K, Nishiyama R, Takaya Y, Ishikawa T. Is a high serum copper concentration a risk factor for implantation failure? BMC Research Notes 2017 Aug 10; 10(1): 387.
3. Pfeiffer R. Wilson's Disease. Semin Neurol 2007; 27(2): 123-32.