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Title:

HETEROZYGOUS BIOTINIDASE DEFICIENCY DOES NOT IMPACT OVARIAN RESERVE, RESPONSE, OR REPRODUCTIVE POTENTIAL

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Objective:

Biotinidase deficiency (BTD) impairs fatty acid and glucose metabolism by reducing utilization of biotin, a B complex vitamin. Knowledge regarding the effect of BTD on human reproductive function is limited; as only animal-based studies have explored the associations between biotin and fertility. Biotin-deficient mice have been reported to have a significant reduction in nuclear estrogen and progesterone receptor mRNA and a decrease in the number of primary and Graafian follicles (Baez-Saldana et al., 2009). Biotin-deficient fruit flies have been reported to have markedly decreased fertility (with a 28% reduction in larvae hatched per egg) compared to biotin-sufficient controls. Heterozygous BTD carriers have been shown to have reduced serum biotinidase levels as compared to non-carriers (Wolf et al., 1983); albeit the impact on human fertility has yet to be explored. Expanded carrier testing of reproductive age women provides the opportunity to identify correlations between genotypic data and phenotypic expression. Given the biological link between biotin and fertility, we evaluated ovarian reserve, response, and cycle outcome in heterozygous biotinidase deficiency patients.

Design:

Retrospective, cohort study

Materials and Methods:

Patients who underwent expanded carrier screening followed by IVF treatment (with or without preimplantation genetic testing (PGT))from June 2012 to March 2018 were included in the study. Only heterozygote BTD carriers and controls that tested negative for all mutations (non-carriers) were evaluated. Baseline demographics, ovarian reserve, IVF laboratory outcomes, embryonic aneuploidy and embryo transfer outcomes were compared between BTD heterozygotes and controls. A sub-analysis, restricted to patients undergoing a euploid frozen embryo transfer (FET), was conducted to assess the effect of BTD 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:

Heterozygous BTD carriers (n=227) 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, BTD heterozygosity did not impact AMH (β= -0.02, p=0.9362) or BAFC (β= -0.15, p=0.7993). Controlling for age and AMH, BTD heterozygosity did not modify oocyte yield (β= -1.15, p=0.1051), fertilization (β=-0.04, p=0.22), blastulation (β=0.02, p=0.45) or embryonic aneuploidy (β=0.03, p=0.43). A sub-analysis, restricted to patients undergoing a euploid FET, compared cycle outcomes in heterozygous BTD carriers (n=74) vs. controls (n=437). Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy, BTD heterozygosity did not impact the odds of implantation (OR 1.25 [95% CI 0.73-2.16], p=0.421), ongoing pregnancy (OR 0.85 [95% CI 0.5-1.43], p=0.53), early pregnancy loss (OR 1.61 [95% CI 0.80-3.24], p=0.18) or live birth (OR 1.43 [95% CI 0.74-2.78], p=0.29).

Conclusion:

While there is compelling data from animal-based studies to suggest detrimental effects of biotin deficiency on fertility, our study is the first to assess the effects of BTD heterozygosity on human ovarian reserve and reproductive outcome. Our findings suggest that despite having a genotype associated with reduced biotinidase enzyme activity, BTD carriers have ART outcomes comparable to non-carriers. Women undergoing ART can be comforted in knowing that a BTD carrier status does not adversely impact treatment outcome. Further research is needed to assess: 1) whether BTD heterozygosity can affect fertility in a non-ART population and 2) the minimal threshold of biotinidase activity below which human reproductive function may be impacted.

Table 1:

	Heterozygous	Controls	p value
Patients	227	1214	
Oocyte age	35.4 ± 5.1	36.1 ± 4.8	0.0699
BMI (m^2)	23.3 ± 4.0	23.7 ± 4.2	0.2250
AMH (ng/ml)	3.7 ± 5.5	3.4 ± 4.1	0.5625
BAFC	11.1 ± 6.8	10.6 ± 6.4	0.4296
IVF cycles	156	945	
Patients undergoing IVF	100	586	
Mature oocytes retrieved	13.9 ± 12.1 (1706)	12.7 ± 9.0 (8828)	0.2909
Fertilization Rate	67.2% (1147/1706)	72.3% (6381/8828)	<0.001
Day 3 embryos	8.2 ± 7.8 (1118)	7.3 ± 6.1 (6116)	0.2086
Day 5 embryos	5.4 ± 6.3 (747)	4.8 ± 4.7 (4071)	0.2858
Blastulation rate	65.1% (747/1147)	63.8% (4071/6381)	0.388447
Embryos biopsied for PGT	5.1 ± 4. (456)	4.1 ± 3.6 (2361)	0.0464
Aneuploidy Rate	43.9% (200/456)	45.6% (1077/2361)	0.49
Single euploid FET cycles	74	437	
Implantation rate	63.5% (47/74)	58.8% (257/437)	0.445949
Ongoing pregnancy rate	56.8% (42/74)	53.3% (233/437)	0.58321
Clinical pregnancy loss rate	10.6% (5/47)	9.3% (24/257)	0.7803
Live birth rate	50.0% (22/44)	41.3% (93/225)	0.287889

References:

1. Báez-Saldaña A1, Camacho-Arroyo I, Espinosa-Aguirre JJ, Neri-Gómez T, Rojas-Ochoa A, Guerra-Araiza C, Larrieta E, Vital P, Díaz G, Chavira R, Fernandez-Mejia C. Biotin deficiency and biotin excess: effects on the female reproductive system. Steroids. 2009
2. Landenberger A1, Kabil H, Harshman LG, Zempleni J. Biotin deficiency decreases life span and fertility but increases stress resistance in Drosophila melanogaster. J Nutr Biochem. 2004 Oct;15(10):591-600.
3. Wolf B, Grier RE, Allen RJ, Goodman SI, Kien CL. Biotinidase deficiency: the enzymatic defect in late-onset multiple carboxylase deficiency. Clin Chim Acta. 1983a;131:273–81.