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Title:

POSITIVE CLASSIC GALACTOSEMIA CARRIER STATUS DOES NOT IMPACT OVARIAN RESERVE

Authors:

Cacchione TA¹; Sekhon L^{1,2}; Gounko D¹; Lee J¹; Copperman A^{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:

Classic galactosemia is an inherited disorder of galactose metabolism caused by mutations in the galactose-1-phosphate uridylyltransferase (GALT) gene. Even with early adoption of the recommended galactose-restricted diet, over 80% of affected females develop Premature Ovarian Insufficiency (POI). While heterozygote carrier females are typically asymptomatic, prior research remains conflicted, especially with regard to subtle effects on ovarian reserve. In a study by Cramer *et al*, female carriers were observed to demonstrate an increased likelihood of infertility and early menopause. Conversely, a Dutch study by Knauff *et al*. found no difference in ovarian reserve when comparing classic galactosemia carriers and controls, but was restricted to classic galactosemia carriers with proven fertility. Thus, we explored the relationship between classic galactosemia carrier status and ovarian reserve in the context of a more ethnically diverse group of patients undergoing fertility treatments.

Design:

Retrospective, cohort study

Materials and Methods:

The study included patients of various ethnic backgrounds who underwent fertility assessment and completed expanded carrier screening between June 2012 and March 2018. Several



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measures of ovarian reserve, including Day 3 Follicle Stimulating Hormone (FSH), Anti-Mullerian Hormone (AMH), and antral follicle count (AFC), were compared between female heterozygote carriers for classic galactosemia and negative controls. Student's t-test and a multivariate linear regression model were used for data analysis.

Results:

Female heterozygous carriers for classic galactosemia (n = 43) were compared to non-carriers (n = 7,777). Baseline demographic factors and measures of ovarian reserve are shown in Table 1. When controlling for age, positive classic galactosemia carrier status was not correlated with Day 3 FSH ($\beta=-0.7$, $p=0.22$), AMH ($\beta=0.04$, $p=0.95$), or BAFC ($\beta=-1.3$, $p=0.18$).

Conclusion:

In a large, single center, ethnically diverse population of women presenting for fertility evaluation and treatment, classic galactosemia carriers do not demonstrate diminished ovarian reserve. Our study provides additional support to the findings published by Knauff *et al* and offers further reassurance to female carriers of classic galactosemia. Future studies should aim to: 1) Confirm our findings and those of Knauff *et al*. with a larger sample size and 2) investigate whether specific GALT variants confer differential effects on ovarian reserve given the considerable allelic heterogeneity observed for this gene. In addition, further studies to help elucidate the causative mechanism of POI in affected females is crucial in order to facilitate better treatment options for these patients.

Table 1:

Comparison of mean age and ovarian reserve markers between galactosemia carriers and controls

	Galactosemia carriers (n=43)	Negative Controls (n=7777)	p value
Age	35.8 ± 4.4 (21.7-43.4)	35.7 ± 5.0 (20.7-49.5)	0.96
Day 3 FSH	7.9 ± 3.6	7.2 ± 3.7	0.24
AMH	3.6 ± 3.9	3.5 ± 4.7	0.86
BAFC	12.3 ± 7.0	10.9 ± 6.8	0.19

References:



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