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

Title:

SMITH-LEMLI-OPITZ DISEASE CARRIERS HAVE NORMAL OVARIAN RESERVE AND RESPONSE TO STIMULATION DESPITE REDUCED CHOLESTEROL BIOSYNTHESIZING ABILITY

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:

Smith-Lemli-Opitz (SLOS) syndrome is an autosomal recessive inborn error of cholesterol synthesis caused by a mutation in 7-dehydrocholesterol reductase (DHCR7), the enzyme that catalyzes the last step in cholesterol biosynthesis. In patients homozygous for the DHCR7 mutation, clinical manifestations occur due to severe cholesterol deficiency and increased collections of toxic cholesterol precursors in the body. Heterozygotes have been demonstrated to have partially reduced enzyme deficiency compared with non-carriers (Shefer et al., 1997). Given that cholesterol is the sole precursor of sex steroid hormones, it is conceivable that partially reduced DHCR7 activity could affect reproductive function. The objective of the study was to examine the effect of SLOS disease heterozygosity on ovarian reserve, response and ART outcome.

Design:

Retrospective, cohort study

Materials and Methods:

Between June 2012 to March 2018, patients underwent expanded carrier screening in preparation for ART treatment. The study included heterozygote SLOS carriers and controls that tested

negative for mutations of the SLOS gene. Baseline demographics, ovarian reserve, IVF laboratory outcomes, embryonic aneuploidy, and embryo transfer outcomes were compared between SLOS heterozygotes and controls. A sub-analysis restricted to patients undergoing single euploid FETs was conducted to assess the effect of SLOS 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:

SLOS mutation carriers (n=55) 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, SLOS heterozygosity did not impact AMH (□=-0.54, p=0.4) or BAFC (□=0.74, p=0.5). Controlling for age and AMH, SLOS carrier status was not seen to impact oocyte yield (□=-0.2, p=0.9), fertilization (□=-0.07, p=0.2), blastulation (□=0.002 p=0.98) or embryonic aneuploidy (□=-0.05, p=0.47). A sub-analysis restricted to patients undergoing single, euploid, FETs compared transfer outcome in heterozygous SLOS carriers (n=23) vs. controls (n=437). Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy, SLOS heterozygosity did not significantly impact the odds of implantation (OR 1.2 [95% CI 0.44-3.28], p=0.7), ongoing pregnancy (OR 0.93 [95% CI 0.34-2.56], p=0.88), live birth (OR 0.5 [95% CI 0.12-2.27], p=0.4), or clinical pregnancy loss (OR 1.64 [95% CI 0.19-14.1], p=0.6).

Conclusion:

In the first study to evaluate the effect of SLOS heterozygosity on female reproductive health, our results demonstrate that carriers have ovarian reserve and ART outcome similar to that of non-carriers. Despite having reduced cholesterol biosynthesis to support steroidogenesis, ovarian response and embryo quality were not adversely affected. A possible explanation is that compensation occurs via alternative pathways of sex hormone production (B-ring unsaturated equine-like steroids derived from accumulated 7-dehydrocholesterol). Alternatively, reduced DHCR7 function may facilitate the production of sufficient cholesterol to support normal reproductive function. Identifying and understanding how perturbations in genes related to lipid metabolism impact reproductive function is essential and should be studied outside of the ART setting to assess whether alterations in steroidogenesis can significant impact menstrual function, ovulation, and the hypothalamic-pituitary-ovarian axis.

Table 1:

	SLOS Mutation Carriers	Controls	p value
Patients	55	1214	
Oocyte age	35.6 ± 6.2	36.1 ± 4.8	0.64
BMI	23.3 ± 4.3	23.7 ± 4.2	0.55
AMH	4.04 ± 5.2	3.4 ± 4.1	0.48
BAFC	10.2 ± 6.7	10.6 ± 6.4	0.76
IVF cycles	28	945	
Patients undergoing IVF	20	586	
Oocytes retrieved	13.3 ± 8.3 (371)	12.7 ± 9.0 (8828)	0.76
Fertilization Rate	80.9% (250/309)	72.3% (6381/8828)	0.0008
Day 3 embryos	8.8 ± 5.8 (245)	7.3 ± 6.1 (6116)	0.21
Day 5 embryos	5.9 ± 4.8 (164)	4.8 ± 4.7 (4071)	0.27
Blastulation rate	65.6% (164/250)	63.8% (4071/6381)	0.56
Embryos biopsied for PGT	4.9 ± 4.1 (102)	4.1 ± 3.6 (2361)	0.36
Aneuploidy Rate	48.0% (49/102)	45.6% (1077/2361)	0.63
Single euploid FET cycles	23	437	
Implantation rate	43.5% (10/23)	58.8% (257/437)	0.15
Ongoing pregnancy rate	39.1% (9/23)	53.3% (233/437)	0.18
Clinical pregnancy loss rate	10.0% (1/10)	9.3% (24/257)	0.54
Live birth rate	45.5% (5/11)	41.3% (93/225)	0.79

References:

1. Shefer S, Salen G, Honda A, Batta A, Hauser S, Tint GS, Honde M, Chen T, Holick MF, Nguyen LB. Rapid identification of Smith-Lemli-Opitz syndrome homozygotes and heterozygotes (carriers) by measurement of deficient 7-dehydrocholesterol-delta-7 reductase activity in fibroblasts. Metabolism 1997; 46(7): 844-50.