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Title:

THE IMPACT OF GAP JUNCTION PROTEIN BETA-2 (GJB2) HETEROZYGOSITY ON ENDOMETRIAL THICKNESS, EMBRYO TRANSFER OUTCOME AND PLACENTATION

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Objective:

Homozygous GJB2 mutations are the most common cause of hereditary hearing loss. The GJB2 gene encodes protein for connexin 26 (CX-26), a component of gap junctions not only in the inner ear, but in uterine luminal and glandular epithelial cells. Normally functioning uterine luminal epithelia is required for endometrial receptivity. In a mouse-model study, targeted inhibition of uterine gap junctions has been shown to disrupt embryo implantation (Siao et al., 2013). By regulating uterine blood flow and placentation, gap junctions have been observed to play a role in the adaptive response to pregnancy (Winterhager et al., 2015). The two syncytial trophoblast layers that form the placental barrier are connected by dense arrays of CX-26 containing gap junctions (Shin et al. 1996). Whether a partial loss of GJB2-encoded CX26 activity impacts human embryo implantation and placentation is currently unknown. The objective of our study was to examine the effect of GJB2 mutation heterozygosity on endometrial thickness and frozen embryo transfer (FET) cycle outcome.

Design:

Retrospective, cohort study

Materials and Methods:

Patients underwent expanded carrier screening, from June 2012 to March 2018. The study included heterozygote GJB2 carriers and controls that tested negative for all mutations. All patients underwent a single, euploid FET. Baseline demographics, cycle characteristics, FET outcomes, and delivery outcomes were compared between GJB2 carriers and controls. 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:

GJB2 carriers (n=53) that underwent 88 FET cycles were compared with non-carriers (n=289) who underwent 437 cycles. Baseline demographic factors, cycle characteristics, FET and pregnancy outcomes are shown in Table 1. Controlling for age and BMI, endometrial thickness was not modified in GJB2 carriers (□=-0.06, p=0.81). Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy, GJB2 carrier status did not modify the odds of implantation (OR 1.05 [95% CI 0.64-1.72], p=0.85). The odds of ongoing pregnancy were increased in GJB2 carriers (OR 1.9 [95% CI 1.03-3.41], p=0.04). In the same multivariate model, clinical pregnancy loss (OR 2.0 [95% CI 0.0.81-4.72], p=0.14) and live birth (OR 0.82 [95% CI 0.41-1.62], p=0.53) were similar among groups. Additionally, gestational age (□=0.06, p=0.9) and infant birthweight at delivery (□=19.8, p=0.87) were not modified in GJB2 carriers.

Conclusion:

Patients who carry a single-allele mutation in the GJB2 gene can be reassured that they are not at an increased risk for implantation failure, preterm delivery, or reduced infant birthweight. Partial activity of the GJB2 gene appears to generate enough CX26 to meet a critical threshold for normal gap junction activity and/or functional redundancy among connexin isoforms. Interestingly, GJB2 carriers were found to have increased odds of ongoing pregnancy, which may be reflective of a possible heterozygote advantage. As more patients undergo expanded carrier screening, larger studies will assess whether this effect is reproducible and reflective of a possible compensatory mechanisms that benefit implantation and pregnancy maintenance.

Table 1:

Comparison of patient demographics, cycle characteristics, embryo transfer and delivery outcomes between GJB2 carriers and controls

	GJB2 Carriers	Controls	
Number of patients	53	289	--
Number of FET cycles	88	437	--
Patient age	35.1 ± 3.6	36.6 ± 3.7	0.0003
BMI	24.3 ± 5.0	23.7 ± 4.0	0.29
Endometrial thickness	9.7 ± 2.2	9.5 ± 2.0	0.48
Proportion of embryos biopsied day 5	63.6% (56/88)	69.6% (304/437)	0.27
Proportion of embryos biopsied day 6	34.1% (30/88)	27.9% (122/437)	0.24
Proportion of embryos biopsied day 7	2.3% (2/88)	2.5% (11/437)	0.89
Implantation rate	58.0% (51/88)	58.8% (257/437)	0.88
Ongoing pregnancy rate	48.9% (43/88)	53.3% (233/437)	0.45
Clinical pregnancy loss rate	17.6% (9/51)	9.3% (24/257)	0.08
Live birth	47.8% (22/46)	41.3% (93/225)	0.42
Birthweight	3401.9 ± 521.4	3445.6 ± 555.4	0.75
Low birth weight	4.5% (1/22)	3.2% (3/93)	0.76
Gestational age	38.3 ± 1.4	38.2 ± 2.0	0.81
Preterm delivery	18.2% (4/22)	17.2% (16/93)	0.91

References:

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