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## **THE MORPHOLOGY OF MOSAICISM: CHARACTERIZING LOW- AND HIGH-LEVEL MOSAIC EMBRYOS COMPARED TO EUPLOID EMBRYOS**

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### **OBJECTIVE:**

The developmental patterns of mosaic embryos have yet to be understood.<sup>1</sup> The aim of this study is to determine whether low and high level mosaic embryos differ from euploid embryos in morphologic characteristics.

### **MATERIALS AND METHODS:**

The study included ovarian stimulation cycles in a single academic institution with preimplantation genetic testing for aneuploidy (PGT-A) from January 2020-March 2021. Trophectoderm (TE) biopsies were analyzed using a modified FAST-SeqS NGS-based PGT method and bioinformatics pipeline. Embryos were classified as euploid if the TE biopsy result contained <20% mosaicism; low level mosaic with 20-40%; high level mosaic with 41-80%; and aneuploid with >80%. The association between morphology (high quality overall grade ( $\geq 4BB$ ) and expansion (Exp), inner cell mass (ICM) grade, and trophoctoderm (TE) grade) and the presence and level of mosaicism as compared to euploid embryos were analyzed using chi-square and multivariable logistic regression.

### **RESULTS:**

A total of 7872 embryos were included, of which 4074 (51.8%) were euploid, 2763 (35.1%) were aneuploid and 1035 (13.1%) were mosaic. The proportion of mosaic embryos graded as high quality was significantly lower than euploid embryos (63.5% vs. 72.1%,  $p < .0001$ ) and significantly higher than aneuploid embryos (63.5% vs. 52.3%,  $p < .0001$ ). Controlling for age and day of biopsy, high quality grade was significantly associated with lower odds of mosaicism compared to euploidy (aOR=0.71, 95% CI 0.61-0.82,  $p < .0001$ ). High quality ICM and TE grades were significantly associated with lower odds of embryo mosaicism compared to euploidy (ICM A vs. C: aOR=0.79, 95% CI 0.63-0.99,  $p = .04$ ; TE A vs. C: aOR=0.55, 95% CI 0.46-0.66,  $p < .0001$ ), while Exp was not. Analyzing low vs. high mosaicism revealed that embryos with high quality overall grade (aOR=1.33, 95% CI 1.02-1.73,  $p = .03$ ), and high quality Exp (6 vs. 4: aOR=1.53, 95% CI 1.04-2.23,  $p = .03$ ) and TE (A vs. C: aOR=1.47, 95% CI 1.07-2.02,  $p = .02$ ) were more likely to have low vs. high mosaicism, while ICM was not associated with level of mosaicism. When comparing low and high mosaics respectively to euploid embryos, embryos with poor TE grade were more likely to be low mosaic vs. euploid (TE C vs. A: aOR 1.56, 95% CI 1.25-1.92,  $p < .0001$ ). There were no differences between Exp and ICM grade in low mosaic and euploid embryos. Embryos with poor Exp, ICM, and TE grade were significantly more likely to be high mosaic vs. euploid (Exp 4 vs. 6: aOR=1.38, 95% CI 1.01-1.88,  $p = .046$ ; ICM C vs. A: aOR=1.39, 95% CI 1.01-1.92,  $p = .049$ ; TE C vs. A: 2.27, 95% CI 1.76-2.94,  $p < .0001$ ).

### **CONCLUSIONS:**



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Mosaic embryos receive lower morphologic grades compared to euploid embryos in a dose-dependent relationship, with high mosaics having lower Exp, ICM, and TE grading compared to euploid embryos while low mosaic embryos differ from euploid embryos in TE grade only.

**IMPACT STATEMENT:**

Low level mosaicism may indicate a milder abnormality confined to the TE while high level mosaicism indicates a more pervasive abnormality. Disparities in grading likely reflect the mechanisms through which low mosaics have improved prognosis compared to high mosaics.

**REFERENCES:**

1. Viotti M, Victor AR, Barnes FL, et al. Using outcome data from one thousand mosaic embryo transfers to formulate an embryo ranking system for clinical use. *Fertil Steril*. 2021 Mar 6:S0015-0282(20)32716-3. doi: 10.1016/j.fertnstert.2020.11.041.