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Oral Presentation

Aneuploidy concordance between trophectoderm and inner cell mass by next-generation sequencing in 100 blastocysts

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Introduction

A number of clinical trials have reported improved IVF outcomes when embryos are previously vetted for chromosomal aneuploidies, and yet a significant percentage of euploid embryos still fail to implant. Conversely, there is mounting evidence of mosaic embryos leading to pregnancies, and there even exist anecdotal reports of aneuploid embryos resulting in healthy births. Critics of PGT-A point out that a TE biopsy might not correctly represent the entire blastocyst. Genetic discordance between TE and ICM could severely affect the clinical outcomes of PGT-A. Furthermore, a blastocyst classified as aneuploid might in reality contain a euploid ICM, which could lead to discarding potentially viable embryos in IVF clinics. To date, studies addressing the question of concordance between TE and ICM have relied on currently superseded technologies and/or small sample sizes. Here we analyze 100 blastocysts that were classified as aneuploid by PGT-A, probing the genetic makup of their paired ICMs using high-resolution NextGen Sequencing (hr-NGS).

Materials & methods

We optimized a method to collect ICM biopsies that are free of TE cell contamination, validated by immunofluorescence for lineage markers. Using this technique we isolated ICM biopsies from 100 blastocysts that had previously undergone clinical PGT-A, and had displayed aneuploidy in their TE biopsies (93 whole chromosome aneuploids and 7 segmental aneuploids). All samples were analyzed by hr-NGS, and resulting karyotype profiles of TE and ICM biopsies were compared. We also developed a bioinformatics approach based on SNP analysis and imputation to confirm that the biopsies of blastocysts with TE-ICM discordance indeed stemmed from the same embryo, excluding the possibility of sample mix-up or contamination.

Results

Comparison of 100 paired TE-ICM karyotypes revealed that a clinical TE biopsy correctly predicts aneuploidy in the ICM in the vast majority of cases. When one or more whole chromosomes were aneuploid in the clinical TE biopsy, the corresponding ICM was aneuploid in 90 out of 93 blastocysts (96.8%). Nonetheless, when the clinical TE biopsy only contained segmental (sub-chromosomal) aneuploidies, the ICM was aneuploid in only 3 out of 7 cases (43%). Combined, and when all types of aneuploidy were considered, an aneuploid TE biopsy correctly predicted aneuploidy in the ICM in 93 out of 100 cases. Of the 7 out of 100 blastocysts that were TE-ICM discordant, the ICM was mosaic in 2 cases and euploid in 5 cases. A second TE biopsy collected from the 7 TE-ICM discordant blastocysts showed concordance with the original clinical TE biopsy in only 2 out of 7 cases (28%).

Conclusions

These findings suggest that TE biopsy, in our hands, largely predicts the chromosome constitution of the ICM and this has significant clinical implications. Concomitantly, the results suggest clinical value of re-evaluating blastocysts deemed ‘aneuploid’ in select cases by TE re-biopsy, particularly in instances of segmental aneuploidies.