Non-invasive prenatal testing (NIPT) in pregnancy after transfer of aneuploid or mosaic embryo

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1. Introduction

The number of patients opting for preimplantation genetic testing for aneuploidy (PGT-A) is increasing. Traditionally, embryo screening was performed on a single blastomere using fluorescent in situ hybridization (FISH). Technological advances, utilizing next generation sequencing for the analysis of several trophectoderm cells, has increased detection of mosaicism in embryos. Reported clinical outcomes of aneuploid and mosaic embryo transfer (MET) range from implantation failure and early loss to healthy birth of an unaffected child. This retrospective study details a case series following the NIPT and clinical outcomes when available for pregnancies with known aneuploid and mosaic embryo transfer.

2. Methods

Maternal blood samples submitted for NIPT testing were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing as described by Jensen et al.[1] MaterniT® 21 PLUS testing included aneuploidies of chromosomes 13, 18, 21, X, Y and selected subchromosomal events. MaterniT® GENOME sequencing data were analyzed using a novel algorithm to detect trisomies and subchromosomal, genome wide copy number variants 7Mb and largerr.

3. Results

Retrospective analysis identified 14 cases of known aneuploid or mosaic embryo transfer. Partial or complete outcome data were available for all but one case. Of the 14 cases with abnormal PGT-A results only three resulted in an abnormal NIPT. Two of the cases reported concordant PGT-A and NIPT results, one trisomy 7 and one mosaic trisomy 15, with discordant diagnostic testing results and normal pregnancy outcome for both. The third case, positive for both mosaic trisomy 21 and mosaic trisomy 15 on PGT-A, reported only positive mosaic trisomy 21 on NIPT and the pregnancy resulted in miscarriage with no additional testing performed. In the remaining cases, 11 negative NIPT results were reported for embryos suspected to have abnormal cell lines on PGT-A. Eight of 11 cases had negative diagnostic testing or healthy term birth reported. Additional case details are provided in **Table 1.**

4. Conclusions

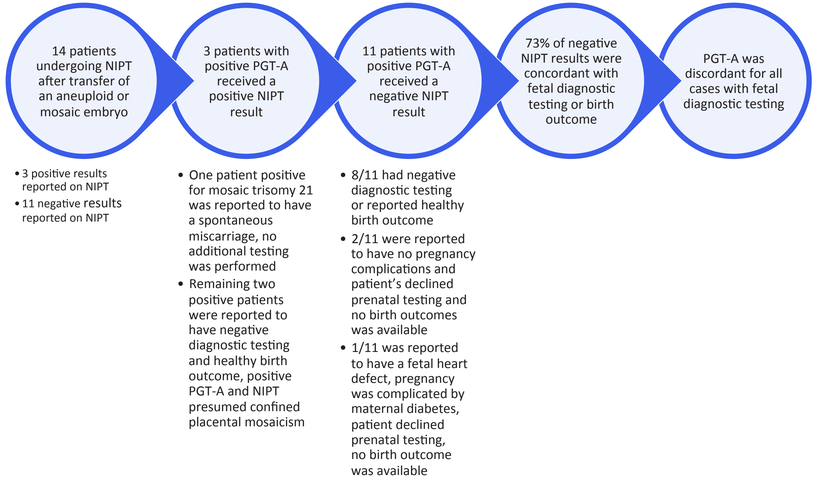
The increased practice of aneuploid or mosaic embryo transfer presents a new challenge for prenatal screening. Ideally, after transfer of an embryo with abnormal PGT-A, diagnostic testing would be pursued. Given the shared biological origin of the placental cfDNA analyzed by NIPT and the trophectoderm cells biopsied for PGT-A, there may be concern that NIPT would simply confirm PGT-A results. In this case series, the NIPT result was negative in 11 of 14 abnormal PGT-A cases. NIPT results were more likely to be concordant with the genetic make-up of the fetus based on diagnostic testing or birth outcome report, **Figure 1**. These findings suggest that genome-wide NIPT may be an option for screening pregnancies with abnormal PGT-A when the patient initially declines diagnostic testing for confirmation of fetal status.

Tables + Figures

Table 1. Clinical case details

	PGT-A Result	NIPT Result	Clinical Information and Outcome
Case 1	Trisomy 7	Trisomy 7	Negative amniocentesis (karyotype; UPD studies). No reported pregnancy complications and normal term delivery of a healthy child.
Case 2	13q deletion (~43 Mb)	Negative	No reported pregnancy complications and normal term delivery of a healthy child.
Case 3	Mosaic monosomy 11	Negative	Negative amniocentesis (karyotype; array). No additional outcome information provided.
Case 4	Mosaic 2q deletion (~45 Mb)	Negative	No additional outcome information provided.
Case 5	Mosaic 13q deletion (~10Mb)	Negative	No reported pregnancy complications and normal term delivery of a healthy child.
Case 6	Mosaic Xq duplication (~46 Mb)	Negative	No prenatal testing. Fetal heart defect noted on ultrasound. Pregnancy complicated by diabetes. No additional outcome information known as patient transferred care.
Case 7	Mosaic monosomy 19	Negative	No reported pregnancy complications. No additional outcome information provided.
Case 8	Mosaic 7p duplication (~55 Mb)	Negative	Negative amniocentesis (karyotype; array). No additional outcome information provided.
Case 9	Mosaic trisomy 15 and 21	Mosaic trisomy 21	Fetal demise reported shortly after screening. No additional testing.
Case 10	Mosaic 4q and 8q deletions (~39 Mb and ~37 Mb, respectively)	Negative	No reported pregnancy complications. Declined amniocentesis. No additional outcome information provided.
Case 11	Mosaic monosomy 7	Negative	No reported pregnancy complications and normal term delivery of a healthy child.
Case 12	Mosaic trisomy 15	Mosaic trisomy 15	Negative amniocentesis (array; UPD studies). No reported pregnancy complications and normal term delivery of a healthy child.
Case 13	Mosaic trisomy 22	Negative	No reported pregnancy complications and normal term delivery of a healthy child..
Case 14	Mosaic monosomy 22	Negative	No reported pregnancy complications and normal term delivery of a healthy child. Postnatal array negative.

Figure 1. Overview of results



References

1. Jensen TJ, Zwiefelhofer T, Tim RC, et al. (2013) High-throughput massively parallel sequencing for fetal aneuploidy detection from maternal plasma. *PLoS ONE* 8(3): e57381. doi:10.1371/journal.pone.0057381

25th ISPD Virtual Annual Conference; 2021 June 6-8.

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