Abstract Details

Session title: Reproductive (epi)genetics
Session type: Poster discussion session
Presentation number: P-595

Abstract title:

Higher resolution aneuploidy screening with targeted NGS may increase the pool of transferrable embryos despite inclusion of segmental and mosaic range diagnostic categories

S. Morin[1], A. Tiegs[2], C. Jalas[3], Y. Zhan[3], J. Landis[3], S. Neal[2], J. Franasiak[2], R. Scott- Jr.[2].
[1]IVI/RMA Northern California, Reproductive Endocrinology and Infertility, San Francisco, U.S.A..
[2]IVI/RMA New Jersey, Reproductive Endocrinology and Infertility, Basking Ridge, U.S.A..
[3]Foundation for Embryonic Competence, Genetics, Basking Ridge, U.S.A..

Study question:

How does the higher resolution of next generation sequencing based aneuploidy screening, inclusive of segmental error and mosaic range diagnostic categories, influence the proportion of transferrable embryos in PGT-A cycles?

Summary answer:
The higher resolution capability of targeted NGS (tNGS) for PGT-A produces fewer whole chromosome aneuploidy calls. If mosaics/segmentals are considered transferrable, more embryos are available.

What is known already:
Euploid embryos, screened with qPCR, have been prospectively demonstrated to produce higher implantation rates than unscreened embryos. Early reports suggest that an embryo diagnosed as euploid with higher resolution NGS platforms produce even higher implantation rates than lower resolution approaches. However, some concern has been raised that inclusion of additional diagnostic categories (segmental and mosaic range) in NGS reports may significantly limit the pool of transferable embryos by reducing the number of euploids available. Given lack of quality data regarding the reproductive potential and long term safety of these embryos, some have suggested limiting their inclusion on clinical reports.

Study design, size, duration:
This was a retrospective cohort study of 13,465 embryos from 2,830 cohorts utilizing tNGS based aneuploidy screening at a single IVF center between July 2016 and November 2017. This represented all PGT-A cycles at the center after the reference laboratory switched from qPCR based PGT-A to a tNGS platform. Aneuploidy screening results were compared to a large, published retrospective cohort of 15,169 embryos analyzed with qPCR based PGT-A in 2014 by our group.

Participants/materials, setting, methods:
Targeted NGS embryos were placed into one of four categories: aneuploid (whole chromosome aneuploidy present), segmental (only abnormality was deletion/duplication), mosaic range (no other whole chromosome or segmental aneuploidy), euploid. Diagnostic results were compared to published 2014 cohort using qPCR / SNP microarray with respect to 1) Percentage aneuploid diagnoses per embryo and 2) Percentage of cohorts with at least 1 euploid available. Relationship between age and each diagnostic category was evaluated by logistic regression.

Main results and the role of chance:
The age of the female partners ranged from 21 to 46 years. The percentage of the 13,495 embryos with aneuploid calls was significantly reduced with tNGS compared to qPCR/SNP microarray (32.4% vs. 41%, $p<0.001$). Mosaicism and segmental rates in tNGS cohorts were 3.6% and 7%, respectively. The no result rate was significantly lower with tNGS than the qPCR/SNP microarray cohort (1.2% vs. 2.8%, $p<0.001$).
A total of 80.7% of the 2,830 tNGS cohorts featured at least one euploid embryo for transfer. The likelihood that a cohort produced all aneuploid embryos increased as the age of the female partner

increased ($p<0.001$). However, more than 90% of cohorts produced at least one euploid embryo for transfer for all ages <35 years; 80% of cohorts did so through age 38. It wasn't until age 42 that the majority of cohorts produced no euploid embryos for transfer. The percentage of cohorts in which the only available embryo for transfer was segmental or mosaic was 1.3 and 2.5%, respectively. Thus, 96.2% of cohorts produced a clear clinical strategy (euploid available or all aneuploid embryos).
Female age was strongly associated with whole chromosome aneuploidy. However, there was no association between age and segmental or mosaic range diagnoses.

Limitations, reasons for caution:
These data reflect the experience of one PGT-A strategy. While NGS-based methods are now widely used, the amplification strategy, opportunity for concomitant genotyping, bioinformatic customization, and thresholds for intermediate calls can vary widely. This may explain wide variation in reported prevalence of mosaicism. Higher mosaicism rates may alter these conclusions.

Wider implications of the findings:
If segmental and mosaic range embryos are considered for transfer, the pool of eligible embryos is increased with tNGS (despite inclusion of additional abnormal diagnostic categories), as whole chromosome aneuploidy calls are less frequent. Data from nonselection studies are needed to define reproductive potential and health outcomes of these embryos.

Trial registration number:
Not applicable

Keywords:
Mosaic
Segmental aneuploidy
Preimplantation genetic testing for aneuploidy
Next generation sequencing
qPCR