Session title: Session 71: About how sperm quality and male infertility relate to genetics
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Abstract title:

The influence of poor semen parameters on embryonic chromosome segregation

Biography

Elpida Fragouli is the Senior Laboratory Director of Juno Genetics in Oxford, UK, and holds a visiting research position at the University of Oxford. The genesis of chromosome abnormalities, design and application of novel methodologies aimed to improve embryological parameters, outcomes after IVF, and identification of patient characteristic traits that could affect fertility are Dr. Fragouli's main research interests. Dr. Fragouli has published more than 150 peer-reviewed papers, abstracts, and book chapters, and has won several awards for her work, including the ESHRE basic science prize.

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Study question:

Is male factor infertility associated with an altered incidence of chromosomal abnormalities of potential relevance to subsequent preimplantation development?

Summary answer:
Male factor infertility is associated with increased mosaic chromosome abnormalities, a potential consequence of the sperm's role in formation of the first mitotic spindle.

What is known already:
Infertility affects one in six couples worldwide with male factors contributing in ~50% of cases. Currently, the relative insensitivity of methods used to assess the competence of male gametes represents a significant limitation in evaluating the likelihood that a sperm sample will produce viable embryos if used for oocyte fertilisation. The close relationship between advancing female age and increasing oocyte aneuploidy rates has been well described. However, the extent to which the male gamete influences the genetics of the early embryo and its subsequent development is less clear.

Study design, size, duration:
331 embryos produced by couples with male factor (MF) infertility (semen sample concentration <5million/ml with/without testicular biopsy or epididymal aspiration) were evaluated, and their cytogenetic status retrospectively compared to that of 1245 embryos derived from infertile couples without MF evidence. Examination involved trophectoderm (TE) biopsy followed by next generation sequencing (NGS) for preimplantation genetic testing for aneuploidy (PGT-A). NGS enabled the accurate identification of mosaic and non-mosaic aneuploidies in blastocysts generated by both patient groups.

Participants/materials, setting, methods:
517 couples having IVF with PGT-A in 12 clinics participated. 69 patients (average female age 38.2 years) underwent PGT-A due to MF infertility. The remaining 448 (average female age 40.2 years) underwent PGT-A due to other indications. Patients were divided into “younger” (MF- 32.8 years, others-33.7 years average female age) and “older” (MF- 39.7 years, others- 40.6 years average female age) for data comparison. A highly validated targeted NGS approach was employed for chromosomal analysis.

Main results and the role of chance:
More MF generated blastocysts were euploid compared with those generated by patients undergoing PGT-A for other indications (49% versus 32%, P<0.001). This is presumably a consequence of lower meiotic error rates in the oocytes of MF couples, due to their lower average female age. Conversely, MF patients generated significantly (P<0.001) more mosaic blastocysts (38%) compared with the remaining patients [17% 95%CI (2.906)], a difference that was detectable in both age groups. This increased mosaicism incidence suggests that the MF generated embryos experience more mitotic errors post-fertilisation. No significant difference (P=0.118) in the incidence of segmental aneuploidies was observed between the two patient groups. Of the 339 abnormalities scored in MF generated blastocysts, 286 (84%) affected whole chromosomes and 53 (16%) affected segments. A total of 1853 aneuploidies were identified in the blastocysts generated by the patients undergoing PGT-A for other indications, and 1624 (88%) affected whole chromosomes, with the remaining 229 (12%) being partial. This finding argues against sperm DNA fragmentation having a possibly detrimental effect after fertilisation. MF infertility patients had a significantly lower no-transfer rate, compared to all remaining patients (16% vs. 39% respectively, P<0.001), presumably a consequence of the higher incidence of euploid embryos in this group.

Limitations, reasons for caution:
Classification was based on TE samples biopsied from blastocysts during PGT-A. As only a fraction of the cells from each embryo are assessed, some mosaic embryos may be incorrectly classified as fully euploid or aneuploid. However, this misclassification is expected to have little impact on the overall conclusions.

Wider implications of the findings:
Poor sperm parameter patients are predisposed to generate mosaic embryos. This predisposition should be discussed during the counselling of couples considering PGT-A due to MF. Sperm centrioles are responsible for the first mitotic spindle organisation. Impaired centriole function in suboptimal sperm might explain the increased post-fertilisation chromosome segregation error rates.

Keywords:
Male factor infertility
blastocyst
chromosome segregation
aneuploidy
mosaicism