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> ⭐ **Abstract title:**
> Segmental insertions and monosomies are linked to developmental arrest.

N. De Munck[1], A. Bayram[1], I. Elkhatib[1], A. Liñán[2], A. Arnanz[1], B. Lawrenz[1], H.M. Fatemi[1].
[1]IVIRMA, IVI Middle East Fertility Clinic, Abu Dhabi, United Arab Emirates.
[2]IVIRMA, IVI Middle East Fertility Clinic, Muscat, Oman.

Study question:

Which genetic abnormalities will prevent blastocyst formation?

Summary answer:
Embryos from which the day 3 cleavage stage blastomeres have segmental insertions or monosomies, have a significantly decreased chance to reach the blastocyst stage.

What is known already:
A major negative selection against aneuploid cells happens during the transition from the morula to the blastocyst stage. When analyzing different morphological or time-lapse parameters, they do not allow us to discriminate between euploid and aneuploid blastocysts. Besides the morphokinetic parameters, chromosomal abnormalities of day 3 cleavage stage embryos have been analyzed for their detrimental effect on development. After fluorescence in situ hybridization (FISH) for a selected number of chromosomes, it was noted that trisomies, extensive mosaicism and monosomy X or 21 reach the blastocyst stage more often.

Study design, size, duration:
A single center retrospective study was performed between April 2016 and January 2017. Patients requiring Preimplantation Genetic Testing for Aneuploidies (PGT-A) by Next Generation Sequencing (NGS) were included. All embryos were cultured in a time-lapse imaging system and biopsy was performed on day 3 of development, which allowed us to perform a fresh embryo transfer as embryo vitrification is prohibited. Segmental or whole chromosome insertions and deletions were registered.

Participants/materials, setting, methods:
Of the 285 embryos biopsied on day 3, the embryo arrest was defined at the blastocyst stage if the embryo failed to cavitate 118 hours post-injection. A logistic regression model was applied using the time to cavitate as the response variable and the different mutations as the explanatory variables, and a p-value <0.05 was considered significant. The reliability of the model was tested by plotting the sensitivity and specificity in a ROC curve.

Main results and the role of chance:
After single blastomere biopsy, the 285 cleavage stage embryos were further cultured until day 5 of development. A total of 103 (36.1%) embryos were euploid and 182 (63.9%) were aneuploid. There was a significant difference in the developmental arrest between euploid and aneuploid embryos (8.7% versus 42.9%; p=0.0001). Segmental insertions and monosomies were found to have a statistically and clinically significant effect on developmental arrest (p=0.0163 and p=0.0075), while chromosomal insertions and segmental deletions were not found to have a statistically significant effect on developmental arrest. In case of segmental insertions, an increase of one extra segmental insertion in any given chromosome increases the odd of arrest by 159%. For chromosomal monosomies, the odd will only increase by 29% for every extra chromosomal monosomy. The area under the ROC curve, indicating the ability of our model to correctly classify embryos with arrest based on their chromosomes, was 0.6573.

Limitations, reasons for caution:
Besides the retrospective design of the study, a higher number of embryos is needed to detect which individual chromosomes show a more pronounced effect on developmental arrest.

Wider implications of the findings:
The results of this study reinforce the use of day 5 biopsy. Not only will euploid embryos have a higher chance to develop to the blastocyst stage, the genetic result obtained with trophectoderm samples is also more reliable as compared to day 3 cleavage stage biopsies.