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Title:

PATERNAL CONTRIBUTION TO EARLY EMBRYONIC DEVELOPMENT IN SEVERE MALE FACTOR PATIENTS

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Objective:

Current evidence suggests that the maternal genome is primarily responsible for embryonic development until the cleavage stage, at which time, expression of paternal genes occurs along with activation of the embryonic genome. Theoretically, sperm could influence earlier post-fertilization events, since defects in the sperm centrosome have the potential to compromise early cell division. Additionally, sperm DNA damage has been shown to adversely affect embryo quality as early as day 2 of development. Evidence regarding the association between severe male factor infertility and embryonic development, embryonic aneuploidy, or clinical outcomes within in vitro fertilization (IVF) cycles utilizing intracytosplasmic sperm injection (ICSI) is contradictory. Thus, we sought to assess the relationship between severe male factor infertility and early embryonic development in an IVF model that includes ICSI and preimplantation genetic testing for aneuploidy (PGT-A).

Design:

Retrospective cohort analysis

Materials and Methods:

Our study included patients at a single academic center who underwent IVF-PGT-A cycles from 2011 to 2019. ICSI was used in all study cases. Patients were divided into 2 cohorts: severe oligospermia (<5 million/mL), and normal semen analyses (SA) (≥5 million/mL). The primary outcome was cleavage rate (CR). Secondary outcomes were fertilization rate (FR), blastulation rate (BR), euploid rate (ER), ongoing pregnancy/live birth rate (OP/LBR), and clinical loss rate (CLR). Student's t-test, chi-squares, and multivariate logistic regression analyses were used for statistical analysis, with $p<0.05$ considered significant.

Results:

A total of 3,029 patients underwent 3,488 IVF-PGT-A cycles during the study period, leading to 4,716 single, euploid frozen embryo transfers. In our unadjusted analysis, the FR and CR were significantly lower in the severe oligospermia group compared to the normal SA group (FR 82.30% vs 77.78%, $p<0.0001$; CR 99.25% vs 98.23%, $p = 0.007$). There were no significant differences in BR, ER, or clinical pregnancy outcomes between the groups. After performing an adjusted analysis that controlled for confounding variables, a significant difference in CR between the oligospermia group and the normal SA group ($\beta = 0.99$, $p = 0.03$) remained.

Conclusion:

In the largest study to date evaluating the association between the paternal genome and embryonic development, we demonstrated that oligospermic samples are associated with impaired early embryo development. Our results provide new insight into the role of the paternal genome in embryonic development prior to activation of the embryonic genome. Future studies should aim to examine more closely paternally-derived genomic actions, including epigenetic factors such as paternal centrosome function, chromatin packaging, or histone modification, which impact successful cell division and growth prior to the cleavage stage in severe male factor patients. Our findings may lead to a better understanding of the ways in which maternal-paternal genomic interactions drive early embryonic development.