THE EFFECT OF INSEMINATION METHODS ON EMBRYO MOSAICISM IN PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A) CYCLES

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Study Question

The aim of this study was to determine if conventional insemination vs. intracytoplasmic sperm injection (ICSI) results in a higher incidence of embryo mosaicism in IVF cycles with PGT-A.

Study Design

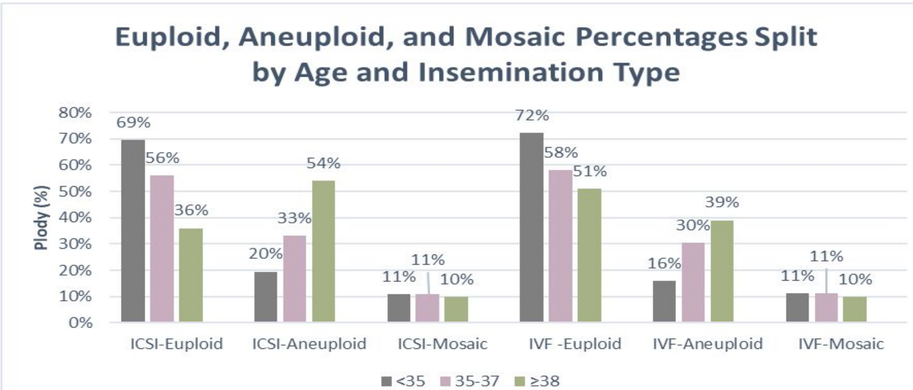
This exempt retrospective chart review was evaluated and approved by the Eastern Virginia Medical School Institutional Review Board before beginning the study. Cycle data were collected for 545 IVF cycles with PGT-A between July 2018 to October 2020 with one of the following methods of insemination: all ICSI (*N* = 369), all conventional insemination (IVF; *N* = 103), or a combination of both ICSI and IVF (COMBO; *N* = 73). A total of 2,672 embryos were biopsied from these cycles, and samples were sent to a single genetics facility for testing with next generation sequencing. Primary outcomes consist of the comparison of euploid, aneuploid and mosaic embryo proportions between combined cohorts and individual cohort comparisons. Secondary outcomes include fertilization, embryo and blastocyst development. Positive chemical pregnancy and clinical intrauterine gestation measures were also used to compare pregnancy outcomes between insemination methods. Aggregate patient data for the number of embryos fertilized, good day 3 development, total blastocyst development, and ploidy status were analyzed by two proportional z-tests. Pearson chi-square test was used for categorical data, such as positive hCG, and two proportional z-tests were used for biochemical loss, clinical uterine gestation (CIG), and implantation rate. A p-value of less than 0.05 was defined as statistically significant, with a 95% confidence interval.

Results

Rates of mosaicism were similar between ICSI and conventional insemination when examining total aggregate data (11% vs. 11%), COMBO cycles, intra-cohort comparison, oocyte age groups, and normal and oligospermic semen samples. A significant difference was only found between embryos from ICSI cycles with testicular or oligospermic samples (17% vs. 9%, p=0.019). Average oocyte age did not vary between insemination type groups, but patients were also grouped by maternal age to compare any differences with the same measured parameters: <35 (N=324), 35-37 (N=130), and ≥38 (N=91). While there were no significant differences in euploid, aneuploid or mosaic rates between ICSI and IVF for the <35 and 35-37 age groups, the ≥38 age group had a significantly higher euploidy rate with IVF compared to ICSI (51% vs. 36%, p=0.043). This significance is also similar to the insemination type comparisons for the total aggregate data (p=0.006), COMBO cycles (p<0.001), and in cycles with normal sperm concentration (p=0.001). However, euploid embryos derived from ICSI vs. IVF did not have a significant difference in chemical pregnancy (63% vs. 67%), biochemical loss (23% vs. 20%), clinical uterine gestation (48% vs. 53%), and embryo implantation (47% vs. 51%).

Aggregate Comparisons	ICSI	IVF
# oocytes inseminated	5,320	2,414
#2PN	4,106 (77)*	1,625 (67)*
Grade ≥6c3 on day 3	3,324 (81)*	1,249 (77)*
# blastocysts total	2,014 (49)	792 (49)
# blastocysts biopsied	1,937	735
# embryo biopsies with results	1,936	731
Euploid	1,204 (62)*	488 (67)*
Aneuploid	524 (27)*	161 (22)*
Mosaic	208 (11)	82 (11)

* Differences within row between columns were significant (p<0.05).



IVF age groups exhibit significantly increased euploidy and decreased aneuploidy compared to ICSI in the ≥38 age group (p<0.05).

Discussion

This study showed that conventional insemination did not have a significant impact on levels of embryo mosaicism. The only significant difference was found between ICSI cycles with testicular sperm or oligospermic samples. Fertilization was lower in testicular cases, perhaps due to lower maturity and competence of testicular sperm. Unfortunately, this area of the study is limited by lower cycle numbers, absence of paternal age data, and the reason for the testicular procedure, such as obstructive or non-obstructive azoo- or oligospermia. The mechanisms that led to the increased aneuploidy in ICSI cycles, as seen in the total aggregate, COMBO and ≥38 comparisons, are unclear at this time. However, this phenomenon could be due to the manipulation of ICSI itself, or to temperature fluctuations affecting meiotic spindle organization. Aneuploidy increases as women age, and this significance may support the idea that more abnormal oocytes are fertilized by the ICSI process. Perhaps the predominant use of ICSI, especially in patients with unexplained infertility and/or normal semen parameters, allows poor-quality oocytes that might not have normally fertilized without ICSI progress to the blastocyst stage, and eventually to trophectoderm biopsy. In our study, euploidy rates for patients with normal semen parameters for ICSI were also lower, further supporting these possible theories. The significance of the results needs to be evaluated further, but they suggest the use of ICSI for cycles with male infertility only. This study provides reassurance that increasing the use of conventional insemination will not lead to a higher incidence of mosaicism.