ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Effect of the male factor on the clinical outcome of intracytoplasmic sperm injection combined with preimplantation aneuploidy testing: observational longitudinal cohort study of 1,219 consecutive cycles

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Objective: To evaluate the impact of the male factor on the outcomes of intracytoplasmic sperm injection (ICSI) cycles combined with preimplantation genetic testing for aneuploidies (PGT-A).
Design: Observational longitudinal cohort study.
Setting: Private in vitro fertilization (IVF) center.
Patient(s): A total of 1,219 oocyte retrievals divided into five study groups according to sperm parameters: normozoospermia (N), moderate male factor (MMF), severe oligoasthenoteratozoospermia (OAT-S), obstructive azoospermia (OA), and nonobstructive azoospermia (NOA).
Intervention(s): ICSI with ejaculated/surgically retrieved sperm, blastocyst culture, trophectoderm-based quantitative polymerase chain reaction PGT-A, and frozen-warmed euploid embryo transfer (ET).
Main Outcomes Measure(s): The primary outcome measures were fertilization, blastocyst development, and euploidy rates; the secondary outcome measures were live birth and miscarriage rates. Perinatal and obstetrical outcomes were monitored as well.
Result(s): A total of 9,042 metaphase II oocytes were inseminated. The fertilization rate was significantly reduced in MMF, OAT-S, OA, and NOA compared with N (74.8%, 68.7%, 67.3%, and 53.1% vs. 77.2%). The blastocyst rate per fertilized oocyte was significantly reduced in MMF and NOA compared with N (48.6% and 40.6% vs. 49.3%). The timing of blastocyst development also was affected in OA and NOA. Logistic regression analysis adjusted for confounders highlighted NOA as a negative predictor of obtaining an euploid blastocyst per OPU (odds ratio 0.5). When the analysis was performed per obtained blastocyst, however, no correlation between male factor and euploidy rate was observed. Embryo transfers also resulted in similar live birth and miscarriage rates. No impact of sperm factor on obstetrical/perinatal outcomes was observed.

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R.M. and D.C. should be considered similar in author order.
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Conclusion(s): Severe male factor impairs early embryonic competence in terms of fertilization rate and developmental potential. However, the euploidy rate and implantation potential of the obtained blastocysts are independent from sperm quality. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)

Key Words: Preimplantation genetic testing, euploid blastocyst, aneuploidy, male factor, azoospermia

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The recent development of assisted reproductive technologies (ART) has allowed in vitro fertilization for many men with severe oligoasthenoteratozoospermia (OAT-S) or azoospermia who were previously excluded from in vitro fertilization (IVF) treatments (1–3). Today, preimplantation genetic diagnosis (PGD) with the use of sophisticated molecular technologies (quantitative polymerase chain reaction [qPCR], single-nucleotide polymorphism array, comparative genome hybridization [aCGH], next-generation sequencing) have been introduced in ART (4–10). PGD is indicated to circumvent the transmission of many known genetic and chromosomal conditions in the parental genotype to the offspring (11–13). It is also well known that both the aneuploidy rate at the blastocyst stage and a successful IVF outcome are strongly correlated with maternal biologic age (14–16). For this reason, preimplantation genetics is increasingly promoted for aneuploidy testing (preimplantation genetic testing for aneuploidies [PGT-A]), especially because of the increased age of the female patient population (17, 18).

Unfortunately, a general international consensus on the indication for PGT-A is still missing. According to Harper et al. (19), indications for aneuploidy testing are: 1) advanced maternal age (AMA, defined as maternal age >37 y); 2) repeated implantation failures (RIF: three or more failed transfers of good-quality embryos); 3) recurrent pregnancy loss (RPL; three or more previous miscarriages); and 4) severe male factor (SMF). SMF remains debatable; Lee et al. (4) limited the indications to only the first three, excluding SMF. Although the literature addresses PGT-A in AMA, the age threshold to consider a woman to be of AMA is still under discussion. In contrast to PGT-A for AMA, there is a lack of scientific data on the application of PGT-A in patients with SMF, which includes azoospermia (both obstructive and nonobstructive), OAT-S, macrocephalic sperm, Klinefelter syndrome, Y-chromosome microdeletion, and even men whose semen analysis does not fulfil the current World Health Organization (WHO) criteria in general.

Contradictory data are reported on the consequences of male-factor infertility on IVF-ICSI outcomes, embryo developmental competence, and incidence of embryo aneuploidy. Regarding the impact of male age, the data are sparse and discordant, and there is not a definite cutoff to consider "advanced paternal age" as an indication for PGT-A. Moreover, there is currently no definition of "advanced paternal age"; most authors considered ≥35 years (20–23), and others ≥40 years (24, 25) and ≥50 years (26).

Certain lifestyle behaviors, such as smoking habits, alcohol and drug consumption, and (mis)use of anabolic drugs, can cause a significant decrease in fertility potential in the couple. But the real impact of these lifestyle habits on ICSI outcome remains unclear (27–29). An increased body mass index (BMI) can cause a significant reduction of the number and motility of spermatozoa (30–32), but its effects on ICSI outcomes remain controversial (30, 33–36).

An increased DNA fragmentation rate can be related to a higher miscarriage rate (37), but some authors warned that it can not be considered to be an independent risk factor for reduced fertilization rate, embryo quality, and pregnancy rate (38, 39).

Finally, other authors (40, 41) showed that SMF may contribute to a higher prevalence of aneuploid embryos in ART. However, this conclusion is mainly based on studies using fluorescence in situ hybridization (FISH) analysis for a limited number of chromosomes on cleavage-stage embryos.

The aim of the present study was therefore to evaluate the impact of the male factor, in terms of sperm parameters, age, BMI, and smoking, on ART outcomes, i.e., fertilization, blastocyst formation, euploidy, and pregnancy rates. Preliminary obstetrical and perinatal outcomes were monitored as well.

MATERIALS AND METHODS

Study Population

This observational longitudinal cohort study involved 1,219 consecutive ICSI cycles performed for 1,090 couples at Genera Center–Clinica Valle Giulia in Rome from April 2013 to December 2015 with the use of qPCR-based PGT-A performed at the blastocyst stage. One year of observation and pregnancy follow-up was included in the study.

The cohort was divided into five groups according to the male partner's sperm parameters, based on the WHO criteria (2010): 1) couples with normozoospermic (N) male partners, accounting for 528 of the 1,219 cycles (43.3%); 2) couples with moderate male factor (MMF), with sperm number ≥5 × 10^6/mL and <15 × 10^6/mL, accounting for 420 cycles (34.5%); 3) couples with OAT-S (sperm number <5 × 10^6/mL) or cryptozoospermia, accounting for 188 cycles (15.4%); 4) couples affected by obstructive azoospermia (OA), accounting for 34 cycles (2.8%); and 5) couples affected by secretory or nonobstructive azoospermia (NOA), accounting for 49 cycles (4.0%).

Genetic analysis was performed for every patient: karyotype, research of CFTR gene mutations, and, in case of azoospermia, Y-chromosome microdeletions. PGT-A was proposed because of: 1) AMA, here defined as ≥35 years; 2) RIF; 3) RPL; or 4) a combination of these conditions.