Reproductive outcomes of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with high levels of DNA fragmentation in semen: systematic review and meta-analysis

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Objective: To compare sperm DNA fragmentation (SDF) levels between testicular and ejaculated sperm and to evaluate outcomes of intracytoplasmic sperm injection (ICSI) with the use of testicular (Testi-ICSI) versus ejaculated (Ejac-ICSI) sperm in nonazoospermic men with high SDF.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Normo- and oligozoospermic men with high levels of SDF in semen subjected to Testi-ICSI or Ejac-ICSI.
Intervention(s): Summary mean difference (MD) and odds ratio (OR) were calculated with the use of an inverse variance model and fixed- or random-effects models, respectively.
Main Outcome Measure(s): Primary outcomes were SDF levels, clinical pregnancy rates (CPRs), and live birth rates (LBRs). Secondary outcomes were fertilization and miscarriage rates.
Result(s): Five studies involving 143 patients provided paired SDF rates for testicular and ejaculated sperm, revealing lower SDF in testicular sperm (MD −24.58%). Four studies involving 507 cycles and 3,840 oocytes reported clinical outcomes of Testi-ICSI and Ejac-ICSI. Fertilization rates were not different between sperm sources, but a trend to lower rates was observed with Testi-ICSI. CPRs were higher for Testi-ICSI than for Ejac-ICSI, as were LBRs, whereas miscarriage rates were reduced with Testi-ICSI.
Conclusion(s): Testicular sperm have lower levels of SDF than ejaculated sperm, with Testi-ICSI for high post-testicular SDF men improving reproductive outcomes compared with Ejac-ICSI. Infertile couples may benefit from Testi-ICSI if male partners have confirmed high SDF in the ejaculate. (Fertil Steril® 2017;108:456–67. ©2017 by American Society for Reproductive Medicine.)
Key Words: Semen, male infertility, intracytoplasmic sperm injection, sperm DNA fragmentation, testicular sperm

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Since its first description in 1992, intracytoplasmic sperm injection (ICSI) has been widely used to overcome all forms of severe male-factor infertility (1). Despite its overall acceptable success rates with the use of abnormal sperm, studies suggest that low sperm quality may adversely affect ICSI outcomes (2–5). The reasons are not entirely understood, but it has been suggested that an underlying genetic component associated with the impaired sperm characteristics may be the leading cause of worse ICSI outcomes with the

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use of abnormal sperm (3, 5). Sperm DNA plays a critical role in normal embryo development, because the genetic information passed on to the next generation depends on its integrity (6–8). Impairment of sperm DNA content has been associated with several conditions, including lifestyle and gonadotoxin exposure, varicocele, male accessory gland infections, advanced paternal age, and systemic diseases (8–14).

Sperm DNA fragmentation (SDF) assays measure the proportion of sperm with damaged chromatin in the neat ejaculate (7). Probes or dyes are used to identify DNA breaks with the aid of fluorescence microscopy, optical microscopy, or flow cytometry according to the method type. Regardless of the analytic method, DNA fragmentation is more common in sperm of infertile men than of fertile counterparts (14–17). Among couples undergoing ICSI, high SDF in the neat semen is found in ~30% of men (18) and is usually associated with abnormal conventional semen parameters (19, 20). High SDF is also a relatively common finding, affecting 20%–40% of infertile men with otherwise normal semen parameters (21, 22).

Recently, SDF testing has emerged as complementary to routine semen analysis. Apart from the ongoing debate regarding the routine utilization of SDF during male infertility workup, recent evidence indicates that SDF may be clinically informative for assisted reproductive technology (ART) outcomes (9, 23–25). Although sperm with fragmented DNA may fertilize an egg with apparently similar efficiency as sperm without DNA fragmentation, the negative impact of a damaged paternal chromatin is usually manifested by impaired embryo development and early pregnancy loss, thus decreasing reproductive success in ART (18, 24–31).

Among many strategies proposed to overcome SDF in couples undergoing ART, the use of testicular sperm in preference over ejaculated sperm has gained increased attention owing to reports of better ICSI outcomes (32–36). The biologic plausibility of using testicular sperm for ICSI in men with high SDF in the ejaculate relies on observations of decreased DNA fragmentation in testicular compared to ejaculated sperm (32, 37). It has been shown that elevated levels of reactive oxygen species (ROS) can cause SDF during sperm transport through the seminiferous tubules and epididymis, thus causing post-testicular harm (38). This oxidation-induced damage to sperm DNA integrity may potentially be avoided in ICSI candidates if the epididymis is bypassed and testicular sperm is used in preference over ejaculated sperm.

Because the clinical decision to revert to testicular sperm instead of using ejaculated sperm for ICSI is debated, and because of the inherent risks and clinical implications of such intervention, the potential role of testicular sperm for ICSI needs to be clarified. Therefore, we examined the available evidence concerning ICSI outcomes for testicular (Testi-ICSI) and ejaculated (Ejac-ICSI) sperm among nonazoospermic infertile men with a strong rationale for using testicular sperm, namely, those patients with confirmed post-testicular SDF.

MATERIALS AND METHODS

This study was exempted from Institutional Review Board approval because it did not involve any human intervention. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement to report the results (39).

Search Strategy

We conducted a systematic search with the use of Pubmed, Scielo, and Google Scholar to identify all relevant studies published until December 2016. The search combined terms and descriptors related to "sperm DNA fragmentation," "sperm DNA damage," "sperm chromatin integrity OR damage," "testicular sperm," "ejaculate," and "intracytoplasmic sperm injection," with the filter "human" in any language. For the advanced search, article types selected were clinical study, comparative study, journal article, cross-sectional study, observational study, case-control study, and randomized controlled trial. We also searched trial registries (http://clinicaltrials.gov and www.who.int/trialsearch).

Eligibility Criteria and Selection of Studies

Articles were included if full texts were available, they enrolled human participants, and they were not review articles. We included studies that compared: 1) ICSI outcomes of Testi-ICSI and Ejac-ICSI among infertile men with high SDF (as defined by each study) in the ejaculate; and 2) SDF rates between testicular and ejaculated sperm of infertile men regardless of whether or not ICSI data were provided. Authors of incomplete datasets were contacted to request their data for this meta-analysis; the dataset from Bradley et al. was provided by the authors because their published paper included outcomes adjusted for maternal age (36). The selection criteria for study inclusion are described in Supplemental Table 1 (Supplemental Tables 1–6 are available online at www.fertstert.org). Exclusion criteria encompassed studies comparing the use of Testi-ICSI and Ejac-ICSI in which the SDF levels were not examined. Two authors (M.R. and S.C.E.) independently assessed all of the abstracts retrieved from the search and obtained full manuscripts of the citations that met the selection criteria. These authors evaluated the studies' eligibility and subsequently extracted the data. Any discrepancies were solved by agreement, and if needed they reached consensus with a third author (N.G.).

The following characteristics were assessed for each study: 1) study population (history of ICSI failure versus no history of ICSI failure); 2) semen analysis profile of participants (oligozoospermia versus normozoospermia); 3) method of SDF testing; and 4) sperm retrieval method. The semen analysis profile was defined according to the mean or median sperm concentration, namely, oligozoospermic (<15 million/mL) and normozoospermic (≥15 million/mL), if not indicated otherwise in the inclusion criteria of each study. All included studies were assessed according to the criteria for nonrandomized studies to evaluate the risk of bias (Supplemental Table 2) (40).