Editorial

Use of sperm DNA fragmentation testing and testicular sperm for intracytoplasmic sperm injection

Chak-Lam Cho[1], Ashok Agarwal[2], Ahmad Majzoub[3], Sandro C. Esteves[4]

[1]Division of Urology, Department of Surgery, Kwong Wah Hospital, Hong Kong, China; [2]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA; [3]Department of Urology, Hamad Medical Corporation, Doha, Qatar; [4]ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil

Correspondence to: Ashok Agarwal. Professor and Director, American Center for Reproductive Medicine, Cleveland Clinic, Mail Code X-11, 10681 Carnegie Avenue, Cleveland, OH 44195, USA. Email: AGARWAA@ccf.org.

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Dr. Ahmad, in his well-written commentary (1), shared his viewpoints about the utility of sperm DNA fragmentation (SDF) testing on each clinical scenario proposed in the practice recommendations by Agarwal *et al.* (2). He highlighted the pitfalls of relying on quantitative semen parameters in current practice and the need for a more reliable diagnostic marker. The author agreed on the value of the practice recommendations in providing well-organized and diverse information for infertility practitioners, while he cautioned against the use of SDF testing as the first choice in routine infertility screening. We wish to expand on this point as well further discuss—the issue on the use of testicular sperm for intracytoplasmic sperm injection (ICSI) in the management of high SDF as raised by Dr. Ahmad.

Infertile couples with ICSI failure represent one of most challenging clinical conditions in the practice of reproductive medicine. The presence of severe abnormality in conventional semen parameters and high SDF in the male partner is not uncommon. High SDF as a cause of ICSI failure is supported by systematic reviews (3,4). The use of testicular sperm seems an appealing treatment option in this group of patients based on the finding of lower SDF in testicular than ejaculated sperm (5,6). On the other hand, there is also concern about the poor motility and fertilizing capacity, and higher aneuploidy rates in testicular sperm which may negatively affect assisted reproduction technology (ART) outcomes (5,7). However, similar pregnancy rates with testicular sperm and ICSI in patients with non-obstructive azoospermia compared with those of ICSI using ejaculated sperm have been reported (8). Early studies have shown promising results in the use of testicular sperm in patients with recurrent ICSI failure. Greco *et al.* reported higher clinical pregnancy and lower miscarriage rates in 18 couples who had at least two previous unsuccessful ICSI. It is demonstrated that SDF rates in testicular and ejaculated sperm were significantly different (4.8% *vs.* 23.6%) (9). A study by Sakkas *et al.* also demonstrated higher implantation and pregnancy rates together with lower miscarriage rate with testicular sperm in 72 patients with SDF of >20% by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) (10). While these studies are often being criticized in view of small sample size and retrospective nature, a recent study provide strong evidence for the use of testicular sperm even in men with elevated SDF subjected to the first ICSI. More importantly, the 5-fold decrease in SDF in testicular sperm did not only decrease the miscarriage rate, but a high live birth rate was reported in the group using testicular sperm with adjusted relative risk of 1.76 (6).

Despite the advantage of using testicular sperm in high SDF (in ejaculated sperm) cases, the use of testicular sperm is not without controversy. Testicular sperm retrieval imposes surgical risk to male partner and extra cost to the ART procedure. It is also argued that another cycle of ICSI with ejaculated sperm in patients with high SDF and repeated ART failures can still achieve clinical and ongoing pregnancy rates of 20% and 15% respectively (11).

Testicular sperm may be particularly valuable in patients with post-testicular source of high SDF (12). SDF may occur during epididymal transit since excessive reactive oxygen species can be generated by epithelial cells of epididymis under physiological stressors and the process of sperm chromatin compaction is still ongoing in the epididymis (13). Therefore, testicular sperm retrieval can effectively decrease SDF in this group of patients by bypassing the epididymis. However, the strategy may not be useful in reducing SDF which occurs in the seminiferous tubules due to intratesticular sperm apoptosis and defects in chromatin remodeling during spermiogenesis (14).

Clearly, more evidence is required to establish the role of testicular sperm in the management of high SDF in ICSI patients. Utilization of testicular sperm in couples with ICSI failure rather than further trial with ejaculated sperm sounds a plausible approach in clinical practice which is also supported by currently available evidence (12). The use of testicular sperm during the first ICSI attempt in men with high SDF (6) is more controversial but represents an important potential indication which may help in better choice of ART technique with high success rate for a particular couple. More importantly, the success of using testicular sperm can be enhanced by improving patient selection. Here, SDF test could play an essential role in identifying infertile men with high SDF. The application of SDF test on ejaculated and testicular sperm on pre-ICSI testicular biopsy may differentiate patients with post-testicular event from those with testicular cause. The application of testicular sperm in managing patients with post-testicular event as the source of high SDF will probably be more effective. Moreover, identification of patients who will fail repeated ICSI with ejaculated sperm may further refine patient stratification. In summary, the use of testicular sperm represents a valuable tool in the management of infertile men with high SDF. More efficient use of testicular sperm depends on appropriate patient selection. This, in turn, may rely on better understanding of SDF and refinement of SDF tests.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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