Editorial

Elucidating the clinical indications of sperm DNA fragmentation in male infertility

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The commentary written by Arafa and ElBardisi on the "Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios" by Agarwal *et al.* (1) is clearly a valid addition to the SDF debate. We agree with the authors that compelling evidence exists signifying the detrimental role of SDF on male fertility (1-3). Semen samples from infertile men tend to have significantly higher levels of SDF, which are associated with a higher likelihood of spontaneous pregnancy loss (4). Furthermore, higher SDF was found to impact success rates of assisted reproductive techniques (ART) through its effect on oocyte fertilization, embryo quality, clinical pregnancy and live birth rate (5,6).

The authors acknowledged the clinical utility of SDF in varicocele as proposed by our clinical guideline article however went further to imply that we suggested the utilization of SDF as a predictor of fertility in this patient population. As such a clarification of intent is necessary to convey the exact message and avoid any misinterpretation. Varicocele is a clinical condition that is commonly prevalent among the male population (7). While its detrimental effect on spermatogenesis has been acknowledged based on the various pathophysiologic mechanisms that have been addressed in our article (1), a good number of men are still able to successfully conceive despite having a clinical varicocele. This has triggered the search for ancillary tests to better select patients in whom varicocele is clinically relevant and who may benefit most from surgical ligation (8). In this context SDF is looked at as a valuable diagnostic tool that can help in decision making and not as a predictor of fertility. Indeed, higher SDF levels have been significantly associated with clinical varicocele and more importantly significant reductions in SDF have been confirmed after varicocelectomy. Esteves *et al.* (9) evaluated SDF in various etiologic conditions of male infertility and observed highest SDF levels among patients with clinical varicocele or leukocytospermia. The systemic review by Zini and Dohle (10) reviewed 511 patients belonging to 12 studies comparing men with clinical varicocele with a control group. A reduction in SDF was reported by all studies after varicocelectomy (10).

Arafa and Elbardisi have proposed modifying SDF recommendation in in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) towards female age. We agree that female age or more importantly oocyte quality is an important parameter to consider in such a clinical scenario. Normal oocytes are capable of repairing sperm DNA damage, however when their repair machinery is compromised sperm with fragmented DNA are expected to perform poorly. Few studies have addressed this aspect such as the retrospective clinical study by Jin *et al.* (11) who investigated 2,865 consecutive couples undergoing IVF or ICSI. The authors utilized three criteria: (I) basal follicle stimulating hormone >10 IU/L; (II) antral follicle count <6; and (III) female age ≥38 years to classify patients into two groups. Group 1, or normal oocyte reserve (NOR) had patients with <2 criteria fulfilled, while group 2, or reduced ovarian reserve (ROR) had patients with >2 criteria

fulfilled. They observed that when SDF measured with sperm chromatin dispersion exceeded 27.3%, it had a statistically significant impact on clinical pregnancy, live-birth, and implantation rates in the ROR group only. Whereas such SDF levels significantly increased the risk of early abortion both in the NOR and ROR groups (11). Nevertheless, while further studies of similar design are still required to settle this issue, it should not influence the proposition that SDF remains clinically relevant in recurrent intrauterine insemination (IUI), IVF and ICSI failures. Why so? Because it guides the fertility specialist to impart timely decisions that should serve to improve the couple's chances for conception (12). Patients with recurrent IUI or IVF failures who are found to have an elevated SDF, are guided towards ICSI, while those with repeated abortions after ICSI can be counseled for the use of testicular sperm instead of ejaculated sperm hoping for better results based on the current clinical evidence (13). Moreover, since the miscarriage rates are higher in couples subjected to both IVF and ICSI when SDF is elevated, so why not test these individuals and propose ways to reduce SDF in the affected men?

As far as environmental exposure is concerned. There is compelling evidence indicating that environmental and lifestyle exposures are associated with a significant increase in SDF (14-17). As such measuring SDF levels during the fertility evaluation of patients with risk factors could serve as a counselling tool for risk prevention and also help monitor patients' adherence to risk avoidance.

In conclusion, SDF is a valuable tool that should aid the fertility specialist propose sound clinical decisions in attempt to improve the couple's fertility outcome. The proper clinical utility of SDF is therefore very relevant, which was the primary focus of the clinical case-scenario guideline article by Agarwal *et al.* (1).

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Footnote

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

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