Commentary

Clinical utility of sperm DNA fragmentation testing: a requisite to infertility practice

Gulfam Ahmad[1,2]

[1]College of Medicine, Prince Sattam Bin Abdulaziz University, Al Kharj, Saudi Arabia; [2]Department of Physiology, University of Health Sciences, Lahore, Pakistan

Correspondence to: Gulfam Ahmad, PhD, MCE, MRD, DIU. College of Medicine, Prince Sattam Bin Abdulaziz University, Al Kharj, Saudi Arabia; Department of Physiology, University of Health Sciences, Lahore, Pakistan. Email: gulfam@uhs.edu.pk.

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Conventional semen analysis is the routine test performed during the evaluation of a couple's fertility status. The test is cost-effective and easy to perform and at the same time provides essential information on quantitative semen parameters such as semen volume, sperm motility, concentration, viability and morphology. Most practitioners consider a male partner normal or abnormal merely looking at a semen report. Notwithstanding that a semen analysis can provide significant information on sperm fertility parameters as predictive for fertilization; it does not forecast sperm functional and qualitative defects such as sperm DNA integrity, oxidative stress and antisperm antibodies (1,2). It also makes decision making difficult for the providers in certain clinical situations because of it's inherit variability (3). Further, the advent of assisted reproductive technology (ART) has revolutionized the infertility treatment by offering, classic In Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) in patients with abnormal semen parameters (4). On the other hand failed Intra Uterine Insemination (IUI), IVF/ICSI cycles and pregnancy loss have been reported in cases where semen parameters were normal (4,5). Additionally, the limitations of conventional semen analysis are extended into unexplained infertility cases where men had normal sperm parameters (6,7).

The above challenges in infertility treatment, over the past few decades, have led the scientists to dig deep into the male gamete in the urge to improve the diagnosis of couple's infertility by providing more effective and reliable diagnostic marker(s). One of such diagnostic markers is sperm DNA fragmentation (SDF). The utility and effeteness of SDF testing is comprehensively described in the paper "*Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios*" (4). This paper provides extensive literature based evidence, a coherent and rational guide on the utility of SDF testing in four different scenarios which every practitioner deals with during his/her practice. In relation to one case scenario, the authors have shown high pregnancy rates after surgical treatment of varicoceles in patients who had high SDF (8,9). Though it warrants further studies, in infertile varicocele patients with borderline to normal quantitative sperm parameters, SDF testing can be helpful in identification of the patients requiring varicocele treatment. SDF testing may be recommended in grade 1 varicocele patients with borderline or abnormal sperm parameters and grade 2/3 with normal semen parameters with the supporting evidence that surgical treatment has significantly improved semen quality and spontaneous pregnancy rates (10).

SDF can be used as an effective tool to identify patients with recurrent pregnancy loss and failed IUI cycles (11,12). This review discusses a scenario of unexplained infertility in a young couple with history of recurrent pregnancy loss. Although controversies exist, strong evidence suggests that unexplained infertility may be caused by high SDF. A significantly higher percentage of population (17.7%) with unexplained infertility has shown SDF index above 30% compared to fertile controls (10.5%) (13). Likewise, higher

SDF index is reported in infertile men with normal semen analysis compared to controls (14). In such cases the authors recommend that SDF should be tested at the earlier which may help in determining the future treatment before going for invasive diagnostic and therapeutic protocols.

In couples where male counterpart exhibits severe sperm abnormalities (oligo-astheno-terato-spermia) ICSI is considered a treatment of choice. Authors have reported a scenario of such couple that underwent ICSI after failed IVF cycles. Clinical pregnancy was achieved following ICSI cycle but 10 weeks later miscarriage occurred. During spermatogenesis spermatozoa have to travel a long way and the possibility of SDF increases during the sperm epididymis transit. In men with severe sperm abnormalities the likelihood of this insult is further increased because of poorly developed defense systems. To address this issue the authors suggest using testicular instead of ejaculated spermatozoa because testicular spermatozoa have shown lower SDF and higher pregnancy rates compared to ejaculated ones (15) and have resulted in lower miscarriages and higher live births (16). Nevertheless, the recommendation on this issue lacks good quality of consistent randomized trials and is based on prospective, cohort and retrospective studies, case series and expert opinions which provides weak arguments in this favor.

In the last scenario, authors point out a case of male with history of 6 years primary infertility and long term exposure to pesticides. The role of environmental and occupational factors and their impact on reproductive health is a burning issue of present era. In current life style it is practically impossible to go even an hour without coming in contact with multiple types of endocrine disrupting chemicals (EDC's). These compounds are ubiquitous not only in the environment through natural means and pesticides, but they are also highly prevalent in commonly used day to day objects. For example, they are used in the production of gelling agents, lubricants, credit cards, food containers, notebooks, paperclips, tape, and many types of clothing, cosmetics, nail polish, shampoo, children's toys, and pacifiers. The exposure of human body to these compounds has been shown to disrupt the endocrine system and thereby affect the proper functioning and development of the male reproductive system. These compounds interfere at several levels preventing the hormones synthesis, transportation or binding at the target organ/tissue. There is less data on this issue and more studies are essentially required to investigate the role of such compounds on reproductive health. Bisphenol A, a widely used EDC, has shown direct *in vitro* correlation with its concentrations and SDF (17).

Smokers (18) and obese (19) men have shown higher SDF than their counterparts. Testicular hyperthermia is yet another important factor associated with higher SDF. A mild increase of only 2 ℃ of testicular temperature has shown increase in SDF assessed by sperm chromatin structure assay (SCSA) in men just after 20 days of hyperthermia treatment. The increase in SDF was observed even before decline in sperm motility and concentration (20). During infertility screening and diagnosis careful history taking is a crucial step. Men who have been exposed to environmental pollutants and occupational hazards, in addition to conventional semen analysis, SDF testing should be advocated. Continuous exposure of EDCs and other life style factors can lead to high SDF which may exhibit transgenerational effects. SDF testing can help practitioners to direct patients to avoid exposure to EDCs and to change their existing life style.

Taken together this review provides well-executed literature support emphasizing the effectiveness and utility of SDF testing in infertility evaluation. Different protocols and testes used in clinical setup by the andrology laboratories have been discussed with their merits and demerits. Although the modern ART treatment has dramatically improved the take home baby rate in infertile couples; the only sperm parameters which cannot be handled by ART is the sperm DNA. The integrity of sperm DNA is a key to successful pregnancy and live birth.

The existing problem in SDF testing is the lack of standard cutoff values, difficulty and variability in the test protocols. Each laboratory has its own reference values and the choice to select a specific protocol remains a debatable issue. Some andrologists prefer Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), others rely on SCSA whereas many are using sperm chromatin dispersion test. SDF testing also requires sophisticated equipment, well trained technicians, expensive reagents, and more time to perform with possible chance of error.

Therefore, this is the peak time to have standard guidelines which can help the fertility practitioner in infertility diagnosis and future therapeutic decisions. The current review provides well-organized and diverse information after digging deep into the literature and has interpreted the conclusion into an easy way by putting up case scenarios which infertility practitioners encounter in their routine professional practice. The guidelines and recommendations set in this paper may serve a landmark to clinicians, urologists and fertility specialists

in understanding the potential advantage of SDF testing in cases of unexplained infertility, recurrent miscarriages, failed IUI, and IVF/ICSI cycles. However, this test should not be the first choice in routine infertility screening due to its cost and financial burden on the patient unless supported by substantial indications.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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