

The price and value of sperm DNA fragmentation tests

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Drs. Fraczek and Kurpisz, in their insightful commentary, highlighted the pitfalls of the current sperm DNA fragmentation (SDF) testing (1). These authors remarked that the association between SDF and clinical outcome of assisted reproduction is not without controversy in the literature. An interesting study cited by these authors proposes the predictive values of sperm vitality on SDF (2) and deserves further discussion in our response.

Semen analysis has been the cornerstone of male fertility evaluation despite its poor predictive value on fertility potential. There is an extensive overlap in conventional semen parameter result between fertile and infertile men (3). Since the release of the first edition of WHO guidelines for semen analysis over three decades ago (4), SDF testing is becoming an important tool for fertility specialists, thanks to the great large number of reports from all over the world. The SDF testing was transformed from a research tool in 1980s to a diagnostic test readily available in clinical andrology laboratories and *in vitro* fertilization (IVF) clinics across the world in the 21st century. Even though the Practice Committee of the American Society of Reproductive Medicine (ASRM) recognized the significance of abnormal SDF on the results of natural pregnancy, intrauterine insemination (IUI), IVF, and intracytoplasmic sperm injection (ICSI) in 2015; its routine use in predicting assisted reproductive outcomes is not recommended (5). Strong correlation between SDF and natural pregnancy is best illustrated by the Danish First Pregnancy Planner Study (6) and the Longitudinal Investigation of Fertility and the Environment (LIFE) Study (7) which unmistakably

demonstrated the negative impact of SDF on time to pregnancy. Couples with a sperm DNA fragmentation index (DFI) of less than 40% by Sperm Chromatin Structure Assay (SCSA) were shown to have 10 times higher probability in achieving natural pregnancy (6). Likewise, an OR of 9.9 (95% CI, 2.37–41.51) was reported in a study correlating SCSA DFI greater than 30% with decreased pregnancy and delivery rates after IUI (8). Although the magnitude of OR seems less impressive, significant OR of around 1.5 on pregnancy rates by IVF and ICSI has been consistently reported (9). More importantly, higher live birth rates after IVF [relative risk (RR) =1.27; 95% CI, 1.05–1.52] and ICSI (RR =1.11; 95% CI, 1.00–1.23) was reported in a recent systematic review and meta-analysis (10). The complexity of human reproductive system with involvement of multiple confounding factors from both male and female partners precludes a simple straightforward test in predicting fertility potential. We feel that it is less important to compare which test is better over the other in prediction of natural and assisted conception; rather, it is essential to recognize the distinct and unique nature of SDF tests in assessing the genetic material of male gamete which contributes half of DNA contents of the offspring. We believe that the SDF tests and semen analysis, along with other sperm function tests, should be complementary to each other in providing the best information to fertility specialists and infertile couples. Controversies do exist about the use of SDF test as is the case for almost all other clinical tests in the field of medicine, but the expanding evidence in support of clinical use of SDF tests cannot be

overlooked. The value of SDF tests can only be further affirmed by identifying its suitable role in clinical practice. We believe the practice recommendations by Agarwal *et al.* represents the next logical step forward by proposing the use of SDF tests in certain clinical scenarios based on the current best evidence (11). The value of a tool is often not determined by its nature, but depends on how it is used.

Drs. Fraczek and Kurpisz in their commentary (1) cited the article by Samplaski *et al.* (2) and suggested that sperm vitality may serve as a predictor of the level of SDF. They further commented that the relatively expensive SDF test may not offer additional information compared to a simple test for sperm vitality (2). We, however, beg to differ from these authors and offer a different viewpoint. It has been reported that higher SDF levels were seen in infertile men with idiopathic oligoasthenoteratozoospermia compared to fertile donors (12). Similarly, it is also known that reactive oxygen species (ROS) is considered as the major cause of SDF with positive relationships between these parameters demonstrated in semen samples (13). ROS exerts its detrimental effect on male fertility via various mechanisms including sperm membrane peroxidation, mitochondrial DNA damage and apoptosis of spermatozoa (14). Therefore, it is easy to visualize the correlation between SDF and various conventional semen parameters since both SDF and semen parameters are more commonly affected by ROS at the same time rather than in isolation. In contrast, a decrease in sperm vitality may be the result of ROS-mediated sperm apoptosis. Consequently, the finding of correlation between sperm vitality and SDF is logical and is the result of the association of both factors with ROS. Contrary to sperm vitality test, SDF result directly reflects the quality of sperm DNA content which is unique. This is clearly illustrated by its superior ability to predict pregnancy outcomes; there is a positive correlation between high SDF and impaired embryo quality (15), lower implantation rate (16), higher miscarriage rate (17), and increased risk of pregnancy loss (18). We argue that sperm vitality is a less reliable predictor of post-fertilization events including embryo quality and pregnancy outcomes since it is merely a measure of sperm phenotype. Secondly, recent advances in treatment strategies for high SDF have been advocated and the use of sperm selection techniques and testicular sperm in managing high SDF has been reported (19-21). However, the combination of these techniques with ICSI is costly and not without risk. As a result, SDF tests are essential in identifying the most appropriate patients for treatment. Failure in proper patient selection

carries serious consequences in terms of risk of assisted reproductive technologies (ART) associated with ovarian hyperstimulation and oocyte retrieval in female partner. A failed ICSI cycle also means a significant financial burden to the couple (about \$13,000 in the United States) (22). The study by Samplaski *et al.*, as cited by the authors, calculated that over 32% of men would gain additional information from DNA fragmentation testing since vitality test alone would fail to accurately predict SDF in these patients. Dr. Samplaski stated that vitality testing may represent a cost-saving measure in view of higher cost of SDF testing when compared to vitality testing (2). However, taking into account the direct cost of a failed ART cycle, the extra cost imposed by SDF testing in providing valuable clinical information for management decision can be justified in this sense. The stated value of a clinical test can sometimes be deceiving as the actual expense of a less accurate test result may turn out to be enormous.

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Footnote

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

References

1. Fraczek M, Kurpisz M. Is the sperm DNA status the best predictor of both natural and assisted conception? *Transl Androl Urol* 2017;6:S594-6.
2. Samplaski MK, Dimitromanolakis A, Lo KC, et al. The relationship between sperm viability and DNA fragmentation rates. *Reprod Biol Endocrinol* 2015;13:42.
3. Guzik DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. *N Engl J Med* 2001;345:1388-93.
4. World Health Organization. WHO laboratory manual for the examination of human semen and semen-cervical mucus interaction. 1st ed. Singapore: Press Concern, 1980.
5. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. *Fertil Steril* 2015;103:e18-25.
6. Spanò M, Bonde JP, Hjollund HI, et al. Sperm chromatin damage impairs human fertility. *The Danish First*

- Pregnancy Planner Study Team. *Fertil Steril* 2000;73:43-50.
7. Buck Louis GM, Sundaram R, Schisterman EF, et al. Semen quality and time to pregnancy: the Longitudinal Investigation of Fertility and the Environment Study. *Fertil Steril* 2014;101:453-62.
 8. Bungum M, Humaidan P, Axmon A, et al. Sperm DNA integrity assessment in prediction of assisted reproduction technology outcomes. *Hum Reprod* 2007;22:174-9.
 9. Agarwal A, Cho CL, Esteves SC. Should we evaluate and treat sperm DNA fragmentation? *Curr Opin Obstet Gynecol* 2016;28:164-71.
 10. Osman A, Alsomait H, Seshadri S, et al. The effect of sperm DNA fragmentation on live birth rate after IVF or ICSI: a systematic review and meta-analysis. *Reprod Biomed Online* 2015;30:120-7.
 11. Agarwal A, Majzoub A, Esteves SC, et al. Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios. *Transl Androl Urol* 2016;5:935-50.
 12. Liu CH, Tsao HM, Cheng TC, et al. DNA fragmentation, mitochondrial dysfunction and chromosomal aneuploidy in the spermatozoa of oligoasthenoteratozoospermic males. *J Assist Reprod Genet* 2004;21:119-26.
 13. Henkel R, Kierspel E, Stalf T, et al. Effect of reactive oxygen species produced by spermatozoa and leukocytes on sperm functions in non-leukocytospermic patients. *Fertil Steril* 2005;83:635-42.
 14. Cho CL, Esteves SC, Agarwal A. Novel insights into the pathophysiology of varicocele and its association with reactive oxygen species and sperm DNA fragmentation. *Asian J Androl* 2016;18:186-93.
 15. Morris ID, Ilott S, Dixon L, et al. The spectrum of DNA damage in human sperm assessed by single cell gel electrophoresis (Comet assay) and its relationship to fertilization and embryo development. *Hum Reprod* 2002;17:990-8.
 16. Brahem S, Mehdi M, Elghezal H, et al. Semen processing by density gradient centrifugation is useful in selecting sperm with higher double-strand DNA integrity. *Andrologia* 2011;43:196-202.
 17. Zhao J, Zhang Q, Wang Y, et al. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/ intracytoplasmic sperm injection: a systematic review and meta-analysis. *Fertil Steril* 2014;102:998-1005.e8.
 18. Zini A, Boman JM, Belzile E, et al. Sperm DNA damage is associated with an increased risk of pregnancy loss after IVF and ICSI: a systematic review and meta-analysis. *Hum Reprod* 2008;23:2663-8.
 19. Bradley CK, McArthur SJ, Gee AJ, et al. Intervention improves assisted conception intracytoplasmic sperm injection outcomes for patients with high levels of sperm DNA fragmentation: a retrospective analysis. *Andrology* 2016;4:903-10.
 20. Esteves SC, Sánchez-Martín F, Sánchez-Martín P, et al. Comparison of reproductive outcome in oligozoospermic men with high sperm DNA fragmentation undergoing intracytoplasmic sperm injection with ejaculated and testicular sperm. *Fertil Steril* 2015;104:1398-405.
 21. Arafa M, AlMalki A, AlBadr M, et al. ICSI outcome in patients with high DNA fragmentation: testicular versus ejaculated spermatozoa. *Andrologia* 2017. [Epub ahead of print].
 22. Chambers GM, Adamson GD, Eijkemans MJ. Acceptable cost for the patient and society. *Fertil Steril* 2013;100:319-27.

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