

Insights on the predictive accuracy of the sperm DNA fragmentation tests on male infertility

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Dr. El-Sakka in his commentary on the “Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios” by Agarwal *et al.* (1), has generally acknowledged the importance of clinical scenarios in remedying the current sperm DNA fragmentation (SDF) debate and identifying the proper indications for performing the SDF testing method. He also addressed the current drawbacks of SDF that still impede its routine use in clinical practice. SDF test sensitivity and specificity in predicting male infertility as well as the burden of its cost were among the drawbacks discussed by Dr. El-Sakka in his commentary.

Conventional semen analysis remains the cornerstone of male fertility evaluation. However, despite its ability to provide an overall assessment of male fertility potential, it fails as an accurate predictor of fecundity. Notwithstanding the periodic refinements in semen analysis techniques and cutoff values in the form of WHO guidelines for semen assessment, up to 30% of men with normal semen parameters remain infertile (2). These findings have triggered the search for additional diagnostic tools that could improve our ability to predict pregnancy. Of all the sperm function tests, SDF is perhaps the only test that has withstood the test of time in terms of its applicability in male fertility evaluation. Since the first pioneering publication in *Science* with its cover photomicrograph showing fluorescent flow-cytometric red and green stained sperm and reporting a significant difference in sperm DNA integrity between fertile and subfertile bulls and men (3), the study of sperm

DNA integrity has been constantly evolving. In the years since this first report, several other testing modalities were developed examining different aspects of sperm DNA damage that enhanced our understanding of the paternal genomic contribution to the fetus (1). At the same time, the preponderance of testing modalities having multiple cutoff values have been considered as a disadvantage to the applicability of SDF in clinical practice and was perhaps the principal factor behind failure of reproductive societies to advocate its routine use in the evaluation of male infertility (4). Recently, with the refinements in the testing methodologies and their performance in appropriate clinical scenarios, we are witnessing an improvement in SDF test validity and predictive accuracy (5-7) and are therefore expecting an update to the best practice recommendations.

For example, TUNEL has been found to be a valid independent test of fertility capable of predicting pregnancy both naturally and after ART with a sensitivity of 85% and a specificity of 89% (8). A sperm chromatin dispersion (SCD) test cutoff value of 25.5% was found to have a sensitivity of 86.2% and a negative predictive value of 72.7% ($P=0.02$) in predicting successful ART treatment (9). Likewise, a sperm chromatin structure assay cutoff value of 30% was found to carry a significant predictive power to the likelihood of pregnancy both *in vivo* and after ART, where patients with a SDF <30% were 7.1 times [95% confidence interval (CI), 3.37–14.91] more likely to achieve a pregnancy *in vivo* and ~2.0 times (95% CI, 1.10–2.96) more likely to achieve pregnancy after ART (10). A recent meta-analysis examining

the diagnostic accuracies of different SDF methods for male infertility reported a TUNEL sensitivity and specificity of 77% and 91%, respectively [area under curve (AUC) =0.95] and a combined sensitivity and specificity for SCD and Comet of 77% and 84%, respectively (AUC =0.85) (7).

Dr. El-Sakka had commented about the controversy that still exists regarding the correlation between SDF measures and semen parameter results. On the contrary, compelling evidence from systemic reviews and meta-analyses has consistently demonstrated a significant negative correlation between these two variables (11-13). Instead, the real question here is not whether SDF correlates well with semen parameters. Rather, if SDF can be utilized as a fertility predictor in different clinical scenarios. Such an influence has been most thoroughly investigated in the setting of ARTs. While Dr. El-Sakka has cited Lin *et al.* (14) who failed to find a significant correlation between SDF (measured with SCSA), high DNA stainability (HDS), and outcomes of *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), the systemic reviews and meta-analyses [reviewed by Agarwal *et al.* (1,12,15-18)] have consistently demonstrated a significant negative association between SDF levels and pregnancy rates with IUI [odds ratio (OR) =9.9; 95% CI, 2.37–41.51; P<0.001] and IVF (OR =1.57; 95% CI, 1.18–2.07; P<0.05) (17), and a significant positive association between SDF levels and miscarriage rate after IVF and ICSI (combined OR =2.48, 95% CI, 1.52–4.04; P<0.0001) (17). These controversies are anticipated in medical literature and can be explained by variations in research methodologies or specifically in this case, the method of SDF testing being utilized.

Cost of a procedure is an important aspect that has to be considered in any treatment decision making. Unfortunately, like most fertility treatments which are not covered by medical insurance, the added cost of SDF testing may impose additional burden on the couple's financial demands. Nevertheless, the expenses for SDF testing are perhaps a fraction of the cost of other fertility treatments such as ART procedures or surgical varicocele ligation. The principle aim of the clinical guideline article by Agarwal *et al.* (1) is to elucidate the circumstances where SDF testing result is most influential on treatment decisions, therefore, consequently on the overall treatment cost. For example, SDF results may aid in a recommendation for ART procedure and/or treatment associated with the highest likelihood of pregnancy thereby eliminating any unnecessary cost from less successful ART modalities. Furthermore, the SDF result would also help in selecting

patients who are most likely to benefit from varicocele ligation eliminating unnecessary surgery.

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Footnote

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

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