Commentary

Practical applications of sperm DNA fragmentation testing and its role in infertility

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The illustrative review and evidence-based guidelines of sperm DNA fragmentation (SDF) testing set forth by contemporary opinion leaders in the field provide readers with a valuable tool for evaluating SDF utility in the modern-day reproductive health practice (1).

DNA within spermatozoa normally reside in a dense formation bound to protamines for protection against oxidative stress and other potentially damaging effects during transport, maintaining viability of the cell. Nevertheless, protamine and antioxidant deficiency along with numerous other unidentified causes occasionally result in loss of DNA molecular integrity contributing to diminished reproductive success. Multiple laboratory tests were recently developed to identify patients with SDF including a gel electrophoresis assay (COMET), a chromatin dispersion test (SCD), a dUTP nick end labeling assay (TUNEL) and a chromatin structure assay (SCSA) (2).

Agarwal *et al.* succinctly summarized these tests for SDF assessment and their respective biomolecular mechanisms as well as appropriately characterized current understanding of the association between DNA integrity and infertility. Their review of four indications for SDF testing using clinical scenarios and current evidence along with expert recommendations provide readers with a key guide for navigating challenging infertility cases such as borderline semen parameters, recurrent pregnancy loss and failed assisted reproductive technology (ART) (1). However, there are parts of this review that warrant further discussion.

The authors present a case study of a 29-year-old male with 3 years of secondary infertility, previous miscarriages and two failed intrauterine insemination (IUI) cycles but normal semen parameters. While such a scenario would undoubtedly trigger conversation about SDF testing in our clinic, the current quality of evidence corroborating this practice is insufficient. As noted by Agarwal *et al.*, the prognostic information which can be gleaned from SDF testing is somewhat limited by poor quality of evidence. The reference cited by the review concluded that semen with 30% or more DNA fragmented sperm were infertile, however, the specificity of their test was only 52% (3). Furthermore, there are few peer-reviewed papers evaluating the correlation between DNA and chromatin damage with natural pregnancy success, and these studies are low in power and do not utilize live births as an outcome. Indeed, mostly level ll-b and level III evidence suggest this association without an established predictive value for SDF (2). However, there is level I evidence in the prospective LIFE (longitudinal investigation of fertility and the environment) study demonstrating SDF is associated with time to pregnancy (4). For IUI, a level II-a study using 30% fragmented DNA as a cutoff successfully associated SDF with lower pregnancy and delivery rates. However, similar studies have failed to corroborate the latter findings (2,5).

Thus, additional prospective studies are necessary to confirm and conclusively define the role of SDF testing for the evaluation and management of male infertility. Both prescribing physicians along with their patients should be made aware of the limitations of SDF testing in addition to the possible advantages. These studies though are admittedly difficult to conduct.

Another important consideration is the financial cost of SDF testing. A literature review searching for an evidence—based cost analysis of SDF testing yielded no results. Given that infertility testing and evaluation is only sporadically covered by insurance plans, further clarity on payment is necessary.

The unfortunate truth is that there is no perfect diagnostic test for male infertility. The limitations of semen analysis are well known, yet despite its low sensitivity and specificity it remains the gold standard due to its low cost, wide availability, and non-invasiveness. In contrast, despite being equally benign, SDF testing has encountered much more resistance for adoption. Indeed, as mentioned previously, there are few high-powered studies and no randomized controlled trials (RCTs) substantiating the association between SDF and subfertility and/or ART failure; nevertheless, level I evidence may not be required for SDF testing to be useful in clinical practice. There is an obvious link between DNA damage and pregnancy outcomes and DNA testing provides unique information that supplements semen analysis results without any redundancy (6,7).

Although we would be hesitant to recommend testing for all patients presenting for infertility management, there may be a role in our clinic for SDF testing men whose partners have had repeated miscarriages, unexplained infertility and/or failed ART cycles. If DFI levels are elevated, a discussion regarding management options is warranted. Due to the protective mechanisms innate to sperm cytoplasm, ICSI have been shown to have better outcomes than IVF for men with SDF (5). Cost of testing and the value of the potential results are also weighed on an individual basis although as SDF becomes ubiquitous with further prognostic validation, we predict insurance packages will begin covering a significant portion of this expense (8).

Overall, the recommendations provided by Agarwal *et al.* are succinct and highly practical for providers managing infertility. Guidelines such as these will encourage the incorporation of SDF testing into practice and provide the impetus for future studies with clinically-relevant outcomes.

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Footnote

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