Commentary

Frontiers in sperm function testing: DNA fragmentation analysis shows promise

Amin S. Herati[1,2], Dolores J. Lamb[1,2,3]

[1]Center for Reproductive Medicine, [2]Scott Department of Urology, [3]Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA

Correspondence to: Amin S. Herati, MD. Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX 77030, USA.
Email: aherati@gmail.com.

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While semen analysis (SA) remains a cornerstone test in the evaluation of the infertile male, it is at best only a crude indication of fertility potential. Semen analyses classify infertile men based on the kind and degree of spermatogenic failure but do little to predict how well a sperm will function *in vitro* or *in vivo*. More importantly, men with normal semen analysis parameters can be infertile and vice a versa. Accordingly, sperm function tests were developed to address these clinical shortcomings of SA.

Among the sperm function tests available are sperm DNA fragmentation (SDF) assays, which assess the packaging quality of haploid sperm DNA and test for biochemical evidence of DNA damage. Sperm DNA is normally super-condensed around nuclear proteins, called protamines, to improve the hydrodynamics of the sperm head while simultaneously protecting the DNA from damage during transit (1). Sperm DNA packaging and integrity can be compromised due to errors in compaction, sheering forces during ejaculation, oxidative stress from accumulating reactive oxygen species, aborted apoptosis or a failure to repair DNA mutations. In this review, Agarwal *et al*. (2) provide clinical practice recommendations for SDF testing specifically for infertile males with varicoceles; idiopathic infertility despite normozoospermia; recurrent pregnancy loss; in cases of recurrent failures of intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI); and in men with lifestyle and environmental exposures.

Agarwal *et al*. (2) recommend SDF testing for men with grade 2 or 3 varicoceles and borderline normal SA results and in men with grade 1 varicoceles if they possess normal SA parameters. Sperm DNA fragmentation testing data may arbitrate the surgical decision making in these patients, particularly for the subset of men with normal or near-normal SA results. Similarly, an opportunity exists to improve the diagnostic evaluation for men who possess sub-clinical varicoceles, which are varicocele veins <3 mm but with reversible flow on Doppler Ultrasound. Sub-clinical veins can have a deleterious impact on reproductive potential. This was recently shown by Cantoro *et al*. (3), who performed a prospective evaluation of 218 men with sub-clinical varicoceles corrected by percutaneous embolization. Embolization of these sub-clinical varicoceles improved sperm concentration, sperm motility and FSH values. Correction of sub-clinical varicoceles also significantly improved clinical pregnancy rates (46.3% *vs*. 11.8%, P=0.01). Given the inherently small size of sub-clinical varicocele veins, application of SDF testing in these men may differentiate the men who will ultimately benefit from varicocelectomy. Further research is required to determine if the presence of sub-clinical varicocele associate with a higher percentage of SDF and if correction results in improved SDF rates.

The authors also recommend SDF testing for infertile couples with recurrent spontaneous abortions and for couples with recurrent failure of assisted reproductive technologies (ART). These recommendations are in contrast to those of the American Society for Reproductive

Medicine (ASRM), which recommends against routine use of the sperm DNA integrity tests in the evaluation of the infertile couple due to SDF testing's low predictive ability of pregnancy outcomes, lack of validation between studies, and overall insufficient evidence correlating sperm DNA integrity and reproductive outcomes (4). Therefore, there is a strong need for more research to standardize SDF assay protocols, threshold values, and establish its role in the evaluation of the infertile couple.

Through an analysis of five different clinical scenarios where SDF testing may influence the medical and surgical decision making, the authors provided compelling recommendations for continued SDF testing. Used appropriately, although not an initial screening test for undiagnosed infertile men, SDF testing provides vital information in the evaluation of the infertile male.

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Footnote

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

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