Commentary

Commentary on clinical utility of sperm DNA fragmentation testing

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Approximately 15% of couples are unable to conceive after one year of unprotected intercourse and a male factor is solely responsible or contributory in approximately 50% (1). Of these couples up to 30% may have unexplained infertility with a normal semen analysis and no obvious reason for their inability to conceive (2,3). Semen analyses alone are difficult to use in clinical decision making due to their inherent variability (4). This limitation extends into a variety of clinical situations including assistive reproductive technique (ART) failure, unexplained infertility in the setting of normal bulk semen parameters, and patients with low grade clinical varicoceles.

For years, experts in the field had limited diagnostic testing to offer these patients. These and other clinical scenarios are addressed in the paper, "*Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios*" (5). The authors present a rational guide to the utility of testing sperm DNA fragmentation (SDF) in various clinical settings and offer guidance on how to treat these patients.

DNA integrity testing is relatively new to the armamentarium of the physician who treats infertile couples. While originally described in 1993, it failed to gain traction as a clinical test due to lack of availability at many labs, expense, and lack of test standardization. In the era of IVF/ICSI, this testing has largely supplanted sperm function tests as an adjunct to semen parameters (4). The authors use four common clinical scenarios to show how SDF can be used. In patients with varicoceles and high SDF, patients had a statistically significant improvement in pregnancy rates after surgical treatment of their varicocele (6,7) and DNA fragmentation may help to identify these patients in whom varicocele ligation would be of most benefit. SDF has been used to identify patients with recurrent pregnancy loss (8) or who have failed IUI (9) and can be used as a predictive tool to identify and effectively stratify patients before they proceed with more invasive ART. In these scenarios, the authors recommend SDF testing and evaluation for IVF/ICSI sooner rather than later if the DNA fragmentation was high. In patients who have already failed IVF or ICSI or had a pregnancy loss after IVF/ICSI with ejaculated sperm, SDF testing can help determine the next steps in treatment. As the authors pointed out, there is an increase in SDF as sperm transit through the epididymis (10). No large randomized controlled trials have attempted to address this, but a couple with a high SDF and failed IVF/ICSI may benefit from IVF/ICSI with testicular sperm extraction rather than undergo more IVF/ICSI cycles with epididymal or ejaculated sperm that may fail due to DNA fragmentation (11). Lastly, SDF may help to identify environmental and lifestyle causes (reversible and irreversible) that affect male infertility. Smoking (12), obesity (13), and occupational

exposures (14,15) can all worsen SDF. In these cases, SDF testing can help predict infertility and monitor response to the lifestyle modification which can improve adherence when patients can actually see how their results change.

Because of the high variability of semen analysis, andrologists have been searching for an adjunct that can help guide clinical decision making. In this review, the authors help to determine scenarios where DNA fragmentation testing may be helpful. In our practice, SDF testing is used routinely in the above clinical situations. With oxidative stress of sperm being caused by so many variables (16), SDF testing gives us a common pathway to measure the effects of oxidative damage and the success of treatments whether that be surgery, antioxidants or lifestyle modification.

Unfortunately, there is not enough data to support routine SDF testing in the male infertility population as it has not consistently been able to distinguish between couples who will or will not become pregnant naturally or with ART when applied to all comers. While many studies have shown that lower SDF was more common in men whose partners became pregnant, there are also patients with high SDF that are able to conceive (17). This controversy has led the American Society for Reproductive Medicine (ASRM) to not recommend the use of DNA fragmentation in the routine workup of the infertile male patient (18). But they do state that the "effect of abnormal SDF on the value of IUI or IVF and ICSI results may be clinically informative".

A second difficulty with using DNA fragmentation routinely is the wide variability of technique and standardization. There are currently at least eight methods that can be used to measure DNA fragmentation directly or indirectly (19). Even the most commonly used tests such as the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and the sperm chromatin structure assay (SCSA) are expensive, complex and require standardization within the population that they are used for. The variety of measurement modalities available, along with the lack of standardization, makes wide adoption of SDF testing difficult, but recent research is beginning to define a gold standard for the type of SDF testing that is most accurate (20). Nonetheless, it is important to remember that semen analysis has its own set of limitations as well (21).

Because it adds independent information to the semen analysis, SDF testing can be helpful in determining the best treatment in many clinical scenarios. As more research continues to show benefit and standardization improves, we believe SDF testing will become more and more common in the workup of the infertile male (22). It should be remembered, however, that this testing is expensive and the patient, not the insurance companies, often carries this burden.

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Footnote

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

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