

## Is sperm DNA fragmentation testing ready for prime time?

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The recent article by Agarwal *et al.* entitled “Clinical Utility of Sperm DNA Fragmentation Testing: Practice Recommendations Based on Clinical Scenarios” is a very timely review on a subject area that has engendered an increasing amount of interest among urologists and reproductive endocrinologists alike (1).

While it is becoming well recognized that male infertility is a common problem, the sperm tests presently in use do not reliably predict fertility in men or the outcomes of treatment (2). There is a pressing clinical need for new tests on sperm parameters to help predict male infertility and outcomes of therapies for male infertility.

The classic semen tests measured the basic sperm parameters such as count, motility and the sperm morphology (3). Recently there has been a move to better understand the DNA quality and the impact this might have on male reproductive health (3). One of the areas of biggest interest has been this study of sperm DNA quality using measures of sperm DNA fragmentation.

This increasing interest has been manifested with a dramatic increase in the number of publications on the topic of sperm DNA fragmentation. A Medline search using the Pub Med search engine with the search terms “sperm” and “DNA fragmentation” reveals close to 1,700 articles published on the topic of sperm and DNA fragmentation since 1990. However the number of publications has increased dramatically in the recent years. During the 1990s there are less than 100 articles in total published on the topic of while in 2016 alone over 120 publications were identified.

This dramatic increase in the number of publications on the area has made it challenging for many clinicians to remain up to date on the topic of sperm DNA fragmentation. Many clinicians will have questions about the different methodologies used to measure sperm DNA fragmentation, which patients might benefit from this test, the implications of abnormal sperm DNA fragmentation rates and therapies that could potentially benefit patients with high or abnormal rates of sperm DNA fragmentation.

The paper by Agarwal *et al.* provides an excellent summary of the different types of tests now being used for the detection of sperm DNA fragmentation (1). The summary is very clearly presented and provides the readers with an excellent comparison table of the different kinds of assays presently available.

The question remains: is sperm DNA fragmentation testing clinically useful in 2017?

Unfortunately, there are significant problems with standardization for testing for sperm DNA integrity (1,2). While there are number of tests which measure things such as the single-stranded DNA levels within sperm, protamine deficiency as a marker of sperm DNA quality and sperm DNA dispersion, one of the overriding issues in clinical care is that these tests are often not standardized. While in general a sperm chromatin structure assay result may correlate extremely well with a sperm DNA tunnel assay result, there are difficulties comparing labs since there is significant inter-observer variability noted as well as standardization between laboratories.

This different type of available tests has made it

difficult to compare studies which use different tests and compounding this, the testing laboratories may not standardize their tests in the same way. This makes comparisons between research studies challenging and as a result makes any assertions about the value of any sperm DNA testing difficult to conclusively demonstrate.

Despite the above, there is now compelling evidence that lower sperm DNA fragmentation rates are related to improved reproductive outcomes including higher spontaneous pregnancy rates, higher pregnancy rates with intra-uterine inseminations and higher IVF fertilization rates (1,2,4-9). This article by Agarwal *et al.* also provides evidence that sperm DNA integrity is related to a number of different urological conditions such as varicocele or infection (1). We also have growing evidence that specific therapies such as varicolectomy and treatment of infections may result in improvements in sperm DNA fragmentation rates (10-12).

What has limited the use of sperm DNA integrity testing is the lack of a standardized test for DNA integrity and the inability to date to use the specific sperm DNA integrity test result to reliably predict infertility or treatment outcomes for men with infertility (2).

In general, tests are most clinically valuable if cut points are available above or below which the condition or the prognosis is determined. For example, we have now identified a sperm count of 15 million/mL as the lower level of the range for normal men (3).

At present, as written by the Practice Committee of the American Society of Reproductive Medicine (ASRM), the accurate cut points used for the sperm DNA integrity testing have not been determined<sup>2</sup>. While these ASRM guidelines state categorically that there is inadequate evidence to support the use of sperm DNA fragmentation testing, the guidelines also state that there is evidence that higher sperm DNA fragmentation is related to poorer reproductive outcomes.

How do we explain this apparent contradiction of evidence supporting higher sperm DNA fragmentation being associated with poorer reproductive outcomes, but inadequate evidence to support the use of sperm DNA fragmentation testing to predict fertility outcomes? This really is all about how the tests are interpreted and can this interpretation be used to accurately predict reproductive outcomes.

Is it reasonable to try to find cut points for sperm DNA fragmentation tests? It is quite difficult to imagine that we will ever have highly accurate cut points for a DNA

fragmentation assay. For example, many laboratories use a cut point of a DNA Fragmentation Index (DFI as measured by the sperm chromatin structure assay) of 30% to indicate an abnormal DFI. But it remains quite obvious that a man with a DFI of 70% has different reproductive outcomes than a man with a DFI of 30%, yet based on cut points alone, both are considered to have abnormal DFIs.

Rather than cut points, a nomogram to predict the reproductive outcomes of men with different levels of sperm DNA fragmentation, (much in the same way we now have nomograms to predict the outcomes of varicolectomy) would provide clinicians with a much more valuable and accurate way to interpret the sperm DNA fragmentation test results for their patients (13). Without this type of nomogram, physicians will have difficulty accurately interpreting test results for their patients.

Sperm DNA fragmentation testing, whether supported or not by guidelines, is widely used and (unless there is a major change in practice) is here to stay. There is a promising future for clinical testing on sperm DNA: as our ability to interpret the tests improve, sperm DNA testing could help guide testing for men with infertility and tailor fertility therapies. Improving our ability to accurately predict reproductive outcomes based on the sperm DNA testing is critical in order to fulfill this promise.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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