Commentary

Finding the fit: sperm DNA integrity testing for male infertility

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Complementing the medical history and physical examination, the semen analysis has been an essential laboratory test for the evaluation of male fertility for over 50 years. However, the concept that fertility is defined by threshold values of semen parameters is fundamentally flawed (1). At best, the semen analysis suggests that the probability of achieving fertility is lower than normal (2). In addition, the definition of "normal" semen parameters is constantly challenged: witness the five editions of WHO manuals in which fertile semen parameters have been redefined over 36 years (3). Lastly, wide intra-individual variation in semen quality (2), and seasonal (4) and geographic variations (5) further complicate the potential of the semen analysis to predict fertility. So, something better is needed to help us determine male fertility potential.

Enter sperm DNA integrity testing, probably the most significant advance in the laboratory diagnosis of male infertility in 25 years. First published in 1980, the original study evaluated sperm from known sub-fertile bulls and also men attending an infertility clinic and compared it to that from proven fertile bulls and men (6). Infertile bull sperm showed 1.6-fold higher DNA fragmentation rates of proven fertile bull sperm and semen from infertile men showed a comparable 2.25-fold increase in sperm DNA fragmentation compared to fertile sperm. Since its first description, sperm DNA fragmentation has been correlated to fertility in boars and stallions. In fact, to date over 1600 papers have been published on the topic (7).

Although the biologic construct underlying the connection between sperm DNA fragmentation and fertility is sound, its clinical relevance has been more difficult to demonstrate. As revealed in the review by Agarwal *et al.* (8) of several clinical scenarios in which sperm DNA integrity testing can be considered in human infertility, the quality of evidence uniformly leads to level C recommendation, nothing to brag about. It is for this reason that sperm DNA integrity testing has not been recommended by major clinical societies for inclusion in the initial evaluation of male infertility (9,10). Thus, although sperm DNA integrity testing measures a significant biological parameter, its precise role in the infertility evaluation remains unclear. And this is after 15 years of clinical use. Going forward, with time and more research, we will learn precisely where sperm DNA integrity testing fits into the male infertility diagnostic algorithm.

Among the clinical scenarios presented by Agarwal *et al.*, in which sperm DNA integrity testing could be considered, one highly debated, understudied, expensive and clinically invasive situation involves the decision to revert to testicular [testicular sperm extraction (TESE)] sperm instead of epididymal or ejaculated sperm to simply lower the sperm DNA fragmentation rate. Three caveats should be considered when considering testicular sperm retrieval (TESE) in this setting. First, there is no indication to use TESE sperm in cases of failed *in vitro* fertilisation (IVF) or IVF-intra-cytoplasmic sperm injection (ICSI) with ejaculated sperm with normal or unexamined DNA integrity (11). Second, using TESE sperm in cases of unexamined, severely oligospermic semen samples also lacks supporting evidence. Third, realize that there is a genetic "trade-off" when using TESE sperm instead of ejaculated sperm: testicular sperm has chromosomal aneuploidy rates that are 3-fold higher than ejaculated sperm from the same individuals (12).

Despite its unrealized clinical potential, sperm DNA integrity testing may soon take a back seat to rapidly

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emerging, next-generation genomic and epigenomic fertility testing paradigms. It may be that the library of leftover RNA messages within sperm can better describe its fertility potential (13). It also appears that sperm harbor characteristic epigenetic marks that correlate with their fertility potential in both natural conception and assisted reproductive settings (14). One can now imagine a future in which several sperm "functional" tests are available and, along with this, noninvasive sperm sorting technologies that will enable use to choose "healthy" sperm from a population of affected sperm for assisted reproduction.

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Footnote

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

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