Sperm DNA fragmentation and pregnancy outcomes—the jury is still out

There is a growing body of evidence that the sperm DNA fragmentation index (DFI) may have an important role in the evaluation and treatment of subfertile couples across a variety of clinical settings (1). Unfortunately, much of the data are conflicting when considering DFI from any number of perspectives: risk factors for elevated DFI, correlation of elevated DFI with natural conception, and the role of DFI in outcomes of assisted reproductive technology. Given the equivocal data, the recently updated guidelines on male infertility from the American Society for Reproductive Medicine and the American Urological Association recommend DFI not be used in the initial evaluation of the infertile couple but should be considered for couples with recurrent pregnancy loss (2). In this context, Rios et al. (3) performed a secondary analysis of the MOXI trial with a focus on DFI, providing additional data on this important and evolving topic.

The investigators set out to identify the risk factors for elevated DFI among the cohort of oligospermic men initially enrolled in the MOXI trial. Examining DFI as both a binary and continuous outcome, they found that age was a significant risk factor for elevated DFI, which is consistent with much of the prior literature on this topic (4). None of the other sociodemographic or exposure variables studied were significantly correlated with elevated DFI, in contrast to prior literature demonstrating that obesity, tobacco, and other exposures may be important contributors to DFI (1). This may be, in part, due to the small sample size and the lack of quantification for certain exposures (e.g., tobacco, alcohol use).

The study was also somewhat constrained by the inherent limitations of the MOXI data, which the investigators acknowledged (3). Because of the small number of men with elevated DFI and the small number of pregnancies achieved, the findings must be interpreted with caution. For example, although a key finding demonstrated no difference in overall pregnancy or live birth rates between couples with elevated or normal DFI, couples with elevated DFI had paradoxically increased rates of natural conception, which is puzzling. Additionally, the cohort was restricted to men with oligospermia, and data may not be generalizable to the broader population of normospermic men—perhaps elevated DFI is more important for couples with otherwise normal semen parameters.

The most interesting data presented are the comparisons of three commonly used DFI tests performed on the same semen samples. There was a poor (albeit statistically significant) correlation between the tests. In fact, when considering these tests as dichotomous (elevated or normal DFI) outcomes, there was no significant agreement at all. Only 4.1% of men met the criteria for elevated DFI using the Comet assay compared with 45% using the TUNEL assay. In contrast, a recent study from Javed et al. (5) noted a higher correlation among these same tests for DFI. The discrepancy between studies could be partially because of methodological differences (e.g., samples in the current study were cryopreserved before DFI assessment, which could impact the results). The significant variability demonstrated in the current study presents a challenge when choosing and interpreting these tests in the clinical setting. Moreover, the literature on DFI has employed many different tests, and given the poor correlation among them, any interpretation of the literature must take this into consideration.

The role of DFI in the evaluation and treatment of infertility will continue to evolve. Although the current study does not provide definitive evidence regarding the nature of the relationship between DFI and pregnancy, the investigators have nicely demonstrated that future efforts to elucidate this relationship will require a better understanding of the interplay between tests for DFI and the cohorts in whom they are used.

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