

Pros and cons of sperm DNA fragmentation testing: weighing the evidence

Akanksha Mehta

Department of Urology, Emory University School of Medicine, Atlanta, GA, USA

Correspondence to: Akanksha Mehta, MD, MS. 1365 Clifton Road, Building B, Suite 1400, Atlanta, GA 30322, USA. Email: akanksha.mehta@emory.edu.

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Conventional semen parameters are poor predictors of reproductive outcomes, and do not reliably discriminate between fertile and infertile men (1,2). A growing body of evidence suggests that markers of sperm DNA integrity may help differentiate fertile from infertile men, but the clinical value of sperm DNA fragmentation testing remains a matter of debate (3). Although guidelines and best practice statements published by the American Urological Association (AUA), European Association of Urology (EAU) and the American Society of Reproductive Medicine (ASRM) all acknowledge the potential contribution of sperm DNA fragmentation to male factor infertility, they do not recommend the routine use of sperm DNA integrity tests in the evaluation and treatment of infertile couples (4-6).

Agarwal *et al.* recently published a summary of the literature describing the clinical utility of sperm DNA fragmentation assays, in the context of commonly encountered clinical scenarios, including varicocele, idiopathic infertility/recurrent pregnancy loss, IVF/ICSI failure, and normal/minimally impaired semen parameters in the setting of environmental risk factors (7). The authors recommended that sperm DNA fragmentation testing be offered to couples in each of these clinical scenarios, albeit for a different clinical goals. Impaired sperm DNA integrity may facilitate decision making—for example, whether or not to pursue varicolectomy despite minimal impairment in conventional semen parameters, or whether or not to pursue additional fertility treatments after experiencing recurrent pregnancy loss. The authors argue that impaired sperm DNA integrity may also motivate patients to

commit to lifestyle changes such as smoking cessation, and weight loss and exercise. These arguments are based on the assumption that sperm DNA integrity is a consistent and reliable predictor of pregnancy rates and reproductive outcomes, following natural conception, IUI, IVF, or ICSI.

Based on the available evidence, which is derived primarily from uncontrolled cohort studies, infertile men are more likely to have impaired DNA integrity (8). Increased sperm DNA fragmentation is associated with prolonged time to conception (9), lower rates of pregnancy with natural conception (10), IUI (11), IVF (12-14), and ICSI (14,15). One meta-analysis has also demonstrated an association between DNA fragmentation and pregnancy loss (16). However, not all studies have shown consistent results, in terms of association or magnitude of effect (3,5). The recommendations made by Agarwal *et al.* (7) are, therefore, largely based on expert opinion (grade C), which is reflective of the methodological limitations of the studies on this topic.

There are no validated cut points for any of the available sperm DNA fragmentation assays, to allow them to effectively be used as predictors of fertility (5), which limits the ability of these tests to guide management in scenarios such as varicoceles, especially when conventional semen parameters are normal or close to normal. Test sensitivity for predicting pregnancy with IUI has been shown to be less than 25% (3,11), limiting its utility among couples considering IUI. Although a statically significant difference has been found in pregnancy rates after IVF and ICSI among couples with normal and abnormal sperm DNA fragmentation, it is unclear whether this

translates to a clinically meaning difference (13). Test sensitivity for predicting pregnancy with IVF and ICSI also remains low at 40%, which further limits the utility of these tests as a decision tool for patients considering IVF/ICSI (3). Furthermore, sperm DNA fragmentation assays are generally not covered by insurance, adding to out-of-pocket expenses for couples undergoing evaluation and treatment of infertility. Lastly, for the vast majority of patients with idiopathic infertility, there are no proven therapies to improve DNA integrity, and results of sperm DNA fragmentation tests are unlikely to affect management.

There is no doubt that successful human reproduction depends on the inherent integrity of sperm DNA. The current literature demonstrates that sperm from infertile men is more likely to possess DNA damage compared to sperm from fertile men, and that DNA damage may be detrimental to some reproductive outcomes. But our understanding of what constitutes normal and abnormal levels of sperm DNA damage, and the extent to which it affects reproductive outcomes, remains imperfect. Consideration of sperm DNA integrity testing should be undertaken with these limitations in mind.

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Footnote

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

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