

# Routine assessment of sperm DNA fragmentation in clinical practice: commentary and perspective

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## Introduction

A recent review proposed a guideline on the clinical utility of sperm DNA fragmentation (SDF) testing presented by four clinical scenarios in an evidence-based approach (1). This comprehensive review addressed commonly encountered clinical scenarios and provided practice based recommendations. Furthermore, it tried to explain the current indications of SDF testing as well as the management of increased SDF. Certainly, using clinical scenarios will be a useful reference for assisting practicing physicians in identifying the circumstances in which SDF testing is of greatest clinical value.

It is well accepted that the diagnostic potential of conventional semen analysis is limited. However, semen analysis remains the first step and the cornerstone for evaluation of male fertility. The American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) recommended a thorough primary assessment of the infertile man that should contain a detailed medical and reproductive history, a physical examination and no less than two semen analyses (2,3). A real concern is that around 15% of men with normal conventional semen analysis profiles still complain of infertility which might be related to increased SDF (4,5). Many recent studies tried to address this issue and investigated the possible correlation between SDF and conventional sperm parameters (4,5).

Most of studies reported a reversed association between SDF rate and sperm quality (6). On the contrary, several other studies were unable to demonstrate a significant

association between the conventional seminal variables, such as sperm concentration, motility, vitality, morphology and SDF indices (7). The inconsistency among studies regarding the correlations between conventional seminal variables and SDF indices might be caused by several issues: (I) differences in the used procedures for DNA integrity testing; (II) differences in the techniques and applied criteria for assessment of the analysis of conventional semen parameters; (III) quality control in semen parameters testing and (IV) the selection criteria of the studied populations are not usually standardized (8,9).

## Association between SDF and clinical parameters

Controversy exceeds the correlation between SDF and conventional sperm parameters to surround other important clinical endpoints such as fertilization rates, embryonic development, implantation, pregnancy and abortion rates and congenital anomalies of the offspring (5,10). Although fertilization has been achieved even in the presence of elevated SDF rates, it is generally believed that there is negative correlation between fertilization and the presence of high levels of SDF (9).

## Considerations regarding routine application of SDF assessment in clinical practice

Although the evaluation of the SDF indices are increasingly used in primary clinical assessment as a unique indicator of

male infertility. The sensitivity, specificity and likelihood ratios of the available tests do not support its routine utilization to estimate the probability of pregnancy in *in-vitro* fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) cycles. On the other hand, the importance of SDF has been recognized in the recent AUA and European Association of Urology guidelines on male infertility (1,11,12). Hence, a more realistic approach should be adopted to identify the population of infertile men who might benefit from this newly-emerged tool of fertility assessment (13). Several studies have rationalized this diagnostic test in the following categories: idiopathic infertile patients with significant morphologic abnormalities i.e., polymorphic teratozoospermia, globozoospermia, large head syndrome, varicocele (9), lifestyle factors, such as smoking (even passive smoking), obesity, diabetes mellitus (14), testicular neoplasia specially that followed chemo- and/or radiotherapy, male carriers of a structural chromosomal abnormality, infertile men who had low gestational rates and low embryonic quality in ART, repeated ART failure, miscarriage and genital tract infection (9).

In cases of unexplained male infertility, several conventional assessments of semen revealed no abnormality in addition to the lack of female factor abnormality, SDF may be of benefit. Sources of sperm with SDF include nuclear remodeling disorders with spermatogenesis and other post-testicular factors. These disorders result in increase of oxidative stress which ultimately lead to damage of the sperm DNA integrity. A value above 25% of the SDF index signifies an acceptable threshold for higher chance of miscarriage and pregnancy failure or longer duration till achieving pregnancy (15). If the primary assessment indicates correctible etiology such as varicocele or leukocytospermia, a prerequisite treatment for these etiologies should be offered, i.e., varicocelectomy or antibiotic therapy. However, in the case of idiopathic infertility increased levels of SDF may rationalize empirical treatment such as antioxidant therapy or lifestyle modifications such as cessation of cigarette smoking, to possibly diminish the underlying damage related to oxidative stress (9). Using testicular sperm rather than ejaculated sperm in men with high SDF, oligozoospermia or recurrent IVF failure was reported (16).

### **Debate: should SDF testing be offered to all infertile men with normal semen profiles?**

On the one hand, most clinicians agree on the limitations of

conventional semen analysis. Since we have a more sensitive molecular test that looks at the paternal genome and can detect molecular anomalies in sperm, why shouldn't we use it as an adjunct to the semen analysis? From the clinical stand point, several studies have shown that about 25% of couples are diagnosed with idiopathic infertility as a result of the limitations of current testing (17). Other studies had shown the benefits of SDF testing and the solid effect of SDF testing on fertilization and early embryo quality (18). If lifestyle modification and medical therapy do not result in achievement of natural pregnancy, therefore, SDF testing may be the test we need to identify couples requiring assisted reproductive technique (19). Certain categories of patient who may benefit from SDF testing are patients who have been heavily exposed to toxicants or radiochemotherapies, cancer patients even before they receive chemotherapy in whom the semen contain a higher level SDF; diabetic patients; male partners of wives with repetitive, unexplained pregnancy loss, or unexplained failure of fertilization (20).

On the other hand, although SDF testing is a promising tool in the evaluation of male infertility, from a consensus point of view, there is still lack of strong evidence for its predictive value thus hindering its recommendation for universal adoption. The problem seems to be mainly related to the characteristics of available studies, which included small and heterogeneous populations and used different methods for SDF testing (21). Furthermore, the American Society for reproductive Medicine Practice Committee guidelines endorsed that more research is needed to reach a final conclusion. In addition, this testing is expensive and, in most of the world, the cost is carried out by the patient (22). Thus, it is hard to confidently reach to a consensus agreement that routine SDF testing is mandatory in evaluation of every infertile male (20).

### **Conclusions and perspective**

The authors had summarized information from numerous previous studies and organized clear and practical guidelines in the format of clinical case scenarios. The suggestions and recommendations are truly valid and provide insight into the clinical circumstances in which the assessment of SDF testing may be crucial. In light of the scientific accumulated data, the coming years may witness additional large scale clinical trials before the available standardized detailed tools of SDF assessment can be fully incorporated in routine clinical practice. Certainly, various important issues such

as optimal assay, protocols applied and thresholds of the clinical relevance and prognostic value of SDF assessment are in need for a global consensus.

A conventional semen analysis is still considered the gold standard of male fertility evaluation especially with the availability of universally accepted rigorous methodology to perform the analysis. The current tools for investigating male factor infertility is still far from ideal however, there is promising novel technology and innovative modalities to improve the well-established diagnostic tools for male infertility. A holistic approach for diagnosis of male factor infertility should be adopted. Physicians may need to review all data in patient's chart during the routine diagnostic workup and the data gained from routine seminal assessment in addition to the SDF testing if available. We expect to witness new methods and technologies that may revolutionize and optimize diagnosis and management of certain etiologies of male factor infertility. The vision of diagnosing spermatozoal genomic integrity in a routine diagnostic male infertility workup may become true in the near future.

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### Footnote

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

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