

Restoration of fertility potential via targeted treatment approach

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Dr. O'Flaherty, in his commentary in response to the practice recommendations by Agarwal *et al.* (1), illustrated two important points that are worth further discussion. Firstly, the author correctly pointed out the low success rate of using *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in bypassing male factor infertility. The negative impact of sperm DNA fragmentation (SDF) on reproductive outcomes was also highlighted and, more importantly, the safety of using poor quality sperm was questioned. Then, the author discussed the treatment strategies of high SDF and identified the shortcomings of current sperm selection procedures. Secondly, the authors described the underlying mechanisms of defective sperm DNA compaction in cancer patients (2).

The remarkable evolution of assisted reproductive technologies (ART) has tremendously changed the outlook of infertility management. While the workup of female partner remains important and becomes the focus of ongoing researches (3), little has changed in the field of clinical andrology over the past three decades (4). The possibility of bypassing the most severe form of male infertility by ICSI drives an increase in its application (5). However, the live birth rate utilizing ICSI alone in the treatment of male factor infertility is only around 30% (6). A change in the treatment strategy for infertile couples is eagerly needed. Attention to and management of male infertility factors should be one of the major steps in improving reproductive outcomes in this group of patients. Although correlation between SDF testing and natural pregnancy/ART outcomes has been reported, a lack of effective treatment for high SDF represents a common critique of SDF testing.

Among the treatment options currently available, ability to improve sperm DNA integrity by varicocele repair has been confirmed in a meta-analysis (7). It represents a targeted treatment strategy via an understanding of the central elements in the pathophysiology of varicocele, i.e., reactive oxygen species and SDF (8). Although a targeted treatment strategy is highly effective and often associated with lower risk and cost, not all etiologies of infertility can be managed with this approach due to various reasons. Sperm selection technique and the use of testicular sperm represent alternatives to reduce high SDF with varying success (9). There is emerging evidence suggesting the efficacy of these approaches in the literature (10). On the other hand, the current techniques are limited by the fact that none of them could completely deselect sperm with DNA damage or aneuploidies and risk of fertilization of oocyte by sperm with high SDF cannot be eliminated (11). Therefore, further studies and refinement is required before widespread use of these techniques in clinical practice. Another concern is that a high SDF test result may only represent the tip of an iceberg. High SDF in a sample reflects poor quality sperm in general. The search of a perfect spermatozoon for ICSI may not be possible, or at least highly ineffective, in such a case when the majority of spermatozoa in the semen sample suffer from defective DNA integrity. Combination with other treatments, including lifestyle modifications and oral antioxidant therapy, may improve the performance of sperm selection and testicular sperm by improving the overall semen quality. Ultimately, better knowledge in the underlying pathophysiology of SDF will facilitate formulation of an effective targeted treatment for our

patients. This will, in turn, achieve the ultimate goal in managing an infertile couple—the restoration of natural fertility potential.

The author also enlightened us on the fertility issue of young cancer survivors in their reproductive age. It is observed that testicular cancer and Hodgkin's lymphoma patients had higher SDF both related to the malignancy and chemotherapy (12,13). It is also noted that different SDF tests may have different performance in detecting SDF in this group of patients. Other laboratory tests, e.g., monobromobimane and chromomycin assays, in assessing DNA compaction may have a role in the evaluation (12). Although the observation in a specific group of young cancer patients may not be generalized to all infertile men, it provides researchers with another facet in studying the nature of SDF and understanding SDF testing methods. The use of SDF in young cancer patients in planning sperm cryopreservation and fertility preservation, indeed, is an important clinical utility of SDF testing. In addition, SDF testing may have a role in counselling post-chemotherapy and irradiated patients on timing to attempt natural conception.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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