Editorial

Reactive oxygen species and sperm DNA fragmentation

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Dr. Dada demonstrated her extensive knowledge about sperm DNA fragmentation (SDF) in her elegantly written commentary with a comprehensive discussion on issues such as genetic health of offspring, value of SDF testing in lifestyle factors, modification of SDF by oocyte, role of sperm preparation, concept of reductive stress, methodology of SDF testing, and use of antioxidant and testicular sperm (1). In our response, we have elaborated on the association between reactive oxygen species (ROS) and SDF which has been mentioned repeatedly in Dr. Dada's commentary.

There is a close relationship between ROS and SDF. SDF can be caused by multiple etiologies including varicocele, infection, advanced male age, heat stress, lifestyle factors, defective protamination, and, sometimes, idiopathic. Many of the above etiologies, but not all, mediated by ROS leading to high SDF and ROS is considered the major cause of SDF (2). This concept is best illustrated by the condition of varicocele. The intimate correlation between varicocele and oxidative stress (OS), the result of imbalance of ROS and protective antioxidant system, was demonstrated by the higher level of ROS and lipid peroxidation products in infertile men with varicocele than infertile men without varicocele (3). Moreover, treatment of varicocele is effective in decreasing both ROS (4) and SDF (5).

Elevated ROS levels are present in 30–80% of infertile men and represent a common mediator between various disease conditions and impaired reproductive potential (6). In addition, the implication of ROS on sperm dysfunction by lipid peroxidation of cell plasma membrane, sperm DNA damage and apoptosis in spermatozoa has been reported (7). Although many of the currently available laboratory tests in assessment of ROS and total antioxidant capacity have limitations (8), new recently introduced technologies including oxidation-reduction potential assay provides simpler and more comprehensive measurement of the overall oxidant and antioxidant activities in a semen sample (9).

The apparent cause-effect relationship between ROS and SDF may lead to the false impression that either one of the test is sufficient in assessment of sperm quality. However, each of them actually reflects different aspects of the multifaceted nature of sperm function. A certain level of ROS in semen may not exert the same extent of negative impact on different semen samples. The sequelae of high ROS also depends on the vulnerability of sperm which varies among individuals and is related to integrity of sperm chromatin. On the other hand, SDF tests assess the quality of sperm DNA contents which has a direct correlation with genetic health of the offspring (10). It is evident by the association between high SDF, and impaired embryo quality (11) and increased pregnancy loss (12). While SDF tests specifically assess the DNA content, ROS assays may reflect sperm function from a broader perspective. Elevated ROS levels do not affect sperm nuclear DNA alone, but exert its negative impacts on mitochondrial DNA, cell membrane and apoptotic mechanisms. Therefore, high SDF in a semen sample may occur in face of a normal ROS in patients with defective protamination of sperm chromatin resulting in higher susceptibility of spermatozoa to ROS.

There is no single “magic” test for accurate assessment of fertility potential in face of complex interaction among

numerous factors of both male and female partners in human reproductive system. SDF tests and ROS assays should not stand alone. In contrast, they are complementary to each other and correct interpretation of their results will provide clinicians and patients with valuable information. The same principle should apply to other tests including semen analysis and oocyte quality assessment. A comprehensive assessment of infertile couples and accurate prediction of treatment outcomes can only be made possible with a panel of laboratory tests assessing different aspects of male and female factors. In view of the low success rate of assisted reproductive technologies in bypassing male factors (13) and its associated risk and cost (14), a more precise assessment and correction of reversible male and female factors should be the way to go. Extensive effort of researchers over the last three decades has brought SDF tests from bench to clinic. The expanding evidence in literature will shed more light on the role of SDF assays and others in clinical practice. The practice recommendations by Agarwal *et al.* is an important step in putting forward the potential application of SDF tests in clinical setting (15). We envisage better understanding of the implication of SDF via wider clinical application of the test, which in turn will further expand its clinical indication and benefit a larger number of patients.

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Footnote

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

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