Editorial

The correct interpretation of sperm DNA fragmentation test

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We read the commentary by Dr. Ferlin with interest (1). The author first stated the drawbacks of semen analysis in the diagnosis of male infertility and the need for sperm function tests. It is followed by illustrating the limitation of the current evidence in supporting the routine use of sperm DNA fragmentation (SDF) testing in clinical practice.

The usefulness of SDF tests in the evaluation of male infertility has been questioned and routine use of SDF tests is generally not supported by guideline (2). However, the role of the test as a prognostic marker for natural conception and assisted reproduction is clear. A meta-analysis involving 3 studies and 616 couples revealed that high SDF, determined by Sperm Chromatin Structure Assay (SCSA), was associated with failure to achieve natural pregnancy with an odds ratio of 7.01 (95% CI: 3.68–13.36) (3). Unambiguous relationship between infertility and SDF is demonstrated by the Danish First Pregnancy Planner study using time-to-pregnancy as an endpoint. Fecundability decreased as SCSA DNA fragmentation index (DFI) increased in 250 Danish couples without previous knowledge of their fertility capability (4). Despite the use of different SDF assays, high sensitivity of 80–85% and specificity of 85–90% have been reported with the use of sperm chromatin dispersion (SCD) and terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) in prediction of natural pregnancy (5,6). Although the correlation between SDF and outcome of assisted reproductive techniques is less strong compared with natural conception, evidence is not lacking. Insemination of >12% TUNEL-positive spermatozoa resulted in lack of pregnancy in intrauterine insemination (IUI) (7). A recent study also suggested that SCSA DFI >27% has negative impact on IUI pregnancy rate (8). Odds ratio of around 1.5 has been reported from meta-analyses on correlation between high SDF and *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcomes (9,10). More importantly, the association between SDF and live birth rates was examined in a meta-analysis including 998 couples. Couples whose male partners had low SDF achieved higher live birth rates after IVF (relative risk 1.27, 95% CI: 1.05–1.52) and ICSI (relative risk 1.11, 95% CI: 1.00–1.23) (11). Contrary to Dr. Ferlin's assertion that the use of SDF tests as prognostic markers is still debatable, we encourage correct interpretation of data from another perspective to recognize the value of SDF testing.

Dr. Ferlin commented that most of the SDF assays are not quantitative which represents a drawback of the test. This point deserves more clarification and discussion in our opinion. SDF test result is expressed in the form of percentage sperm with DNA damage crossing a threshold with respect to the total number of sperm. A DFI of 30% does not mean the remaining 70% of sperm is normal. Part of the remaining sperm may be already compromised as regards to DNA integrity, but not yet crossed the threshold detectable by the assay. There is probably a larger portion of the remaining sperm which carry relatively minor DNA damage. The 30% 'positive' sperm only indicate the tip of an iceberg (12). A high DFI should be interpreted as a general poor quality sample instead of an absolute value of abnormal sperm. Dr. Ferlin stated that 'SDF tests do

not measure how much of the sperm DNA in each cell is damaged'. We concur with the statement but think that it is an advantage, rather than a limitation of SDF assays in evaluation of infertile male. In view of large number of spermatozoa and the highly variable DNA integrity of each spermatozoon, quantitative measurement of DNA damage of each spermatozoon is not practical and may not be necessary. The result of SDF assays which reveal the sperm quality of the whole sample in general may be a better indicator in assessment of male fertility. Nonetheless, the usefulness of a clinical test is more dependent on the appropriate application to a specific clinical scenario. On the other hand, we strongly agree with Dr. Ferlin's comment on the importance of distinguishing type and nature of SDF. This knowledge will help us in identifying clinically significant sites of DNA breaks which may better predict reproductive outcome and more research in the area is eagerly awaited.

The author raised another important point on the potential value of oxidative stress (OS) assays in management decisions of infertile men. Indeed, elevated reactive oxygen species (ROS) levels are present in 30-80% of infertile men and represent a common mediator between various disease conditions and impaired reproductive potential (13). We think that SDF and OS assays should be complementary to each other. A high ROS has detrimental effect on sperm DNA content, but the extent of damage depends on the vulnerability of sperm chromatin which varies among individuals. While SDF test result correlates with embryo quality and pregnancy outcomes (14,15), ROS assays may reflect sperm function in a broader perspective due to its negative impacts on various sperm organelles (16). We believe that there is no single test for fertility assessment in view of the complexity of human reproductive system. Semen analysis, SDF tests, OS assays, and possibly other laboratory tests are all essential components and should go hand-in-hand in providing accurate assessment of male fertility. The correct assessment of male fertility by non-invasive tests before deciding to use invasive treatment should benefit infertile couples both clinically and financially.

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Footnote

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

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