Editorial

The role of female factors in the management of sperm DNA fragmentation

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Dr. Varghese *et al.* provided a comprehensive summary of their viewpoint on sperm DNA fragmentation (SDF) (1) in response to the practice recommendations by Dr. Agarwal *et al.* (2). The authors raised the essential question by asking "whether SDF analysis adds useful information which can change the diagnosis or provide a better understanding of the prognosis". Although Dr. Varghese *et al.* considered the predictive value of SDF testing on sperm quality and outcomes of assisted reproductive technology (ART) as still controversial in general, the potential use of SDF in certain circumstances including unexplained infertility was recognized (1). Agarwal and colleagues reached a different conclusion on this issue from another perspective by ascertaining the clinical value of SDF evaluation by summarizing the literature which is more or less the same as those reviewed by Varghese *et al.* (3). Despite the seemingly opposite conclusions, there are actually more similarity than divergence in our opinions. The pitfall of the use of semen analysis in male infertility evaluation, importance of male genome in pregnancy outcomes, limitation of the current SDF testing, and recognition of SDF testing in elucidating the cause of male infertility and directing treatment strategies are only a few of the common viewpoints shared between us. Among the important points raised in the insightful commentary by Varghese *et al.*, we wish to expand the discussion on one point—the role of female factors in the management of SDF.

Varghese *et al.* pointed out the role of oocyte quality in reproductive outcome. The complex interplay between SDF in men and ovarian reserve in women on the clinical outcomes of ART is well illustrated by Jin *et al.* In their retrospective clinical study, the authors reported that the implantation and live birth rates during *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles in women with reduced ovarian reserve were significantly decreased when SDF exceeded 27.3%. While the risk of early abortion was increased in women with normal ovarian reserve in face of high SDF, the implantation, clinical pregnancy and live birth rates were not affected (4). Meseguer *et al.* also demonstrated the potential role of ovarian quality in compensating high SDF. The probability of not achieving pregnancy increased with an increase in SDF when the women's own oocytes were used. However, such a relationship was not observed when donated oocytes from women with proven fertility were utilized (5). As a result, the presence of an intact oocyte repair machinery in good quality oocytes has a pivotal role in reproductive outcomes in addition to SDF. The machinery also serves as a safety check to avoid passage of defective genetic information to offspring. However, not all types of sperm DNA break are repairable (6). It was also shown that there is a capacity of SDF repair and oocyte has the ability to repair less than 8% of sperm DNA damage in an animal model (7). Animal studies reported that female mice with defective DNA double-stranded break repair had increased frequencies of zygotes with sperm-derived chromosomal aberrations when fertilized by sperm with irradiation-induced double-stranded DNA breaks. High embryonic

lethality was observed as a result of the chromosome-type aberration which affects both sister chromatids (8).

The close interaction and delicate balance between SDF and oocyte repair machinery may explain the inconsistent findings from various systematic reviews and meta-analyses on the implication of SDF on IVF/ICSI outcomes as suggested by Dr. Varghese *et al.* The meta-analyses cited by the authors included many heterogeneous studies (9-11). The female factors were not uniformly reported in most of the included studies. This may represent a major pitfall since advanced female age alone may adversely affect oocyte quality leading to impaired capability in SDF repair, among many other factors (5,12).

The complex interplay among numerous male and female factors in human reproduction signifies that an infertile couple should be evaluated together. Successful management of infertile couples requires expertise from various specialties and involves highly sophisticated techniques which can only be made possible in a multidisciplinary team approach. When a new diagnostic tool, for example SDF testing, is evaluated in the clinical setting, the consideration should be based on a couple. The coexistence of multiple male and female factors, reversible or irreversible, in an infertile couple is not uncommon in clinical practice. The result of SDF testing may help the clinicians in prioritizing the timing and sequence of treatment. A high SDF test points to a more significant male factor which warrants earlier interventions. Successful correction of high SDF in infertile men may improve the chance of natural pregnancy or intrauterine insemination (IUI) (3). A more appropriate choice of ART with higher success rate may also reduce the number of treatment cycles of ART (13). The strategy of maximizing the fertility potential and more targeted use of ART reduce the risk and cost implication associated with repeated ART cycles in a couple as a whole.

Indeed, the testing and correction of SDF only reflect one facet of the issue. The deleterious effect of SDF can also be prevented by assessment and improvement of oocyte quality. However, there is a lack of reliable biochemical or molecular markers of oocyte status currently. There are also no widely accepted criteria or grading method for microscopic oocyte morphological evaluation (14). Different clinical studies have used various definitions of oocyte status (4). The success in management of infertile couple must involve optimization of fertility status of both partners. The strategies of maximizing the fertility potential rectify the drawback of ICSI in not only bypassing male factors, but also leave some reversible female factors uncorrected. The approach may provide a safe and economical alternative to ART by achieving natural conception in some couples, and improving the ART outcomes in others.

Further studies are essential not only in SDF but also oocyte quality. Attention to the couple, instead of an isolated infertile man or woman, in both research and clinical settings is of utmost importance in delivering optimal care to our patients. Finally, a clinical practice guideline is not intended to encompass each and every unique clinical case involving multiple factors in real life. The aim of the practice recommendations by Agarwal *et al.* is to promote a better understanding of SDF tests by illustrating the principles with relatively straight forward, but commonly encountered, clinical scenarios mainly concentrating on the male infertility perspective. However, the application of the test should be extended to other more complicated clinical scenarios involving female factors based on the principles, but not limited to those listed in the recommendations.

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Footnote

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

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