Editorial

Sperm DNA fragmentation testing is on the right track

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Dr. Oehninger's elegant editorial dwelled on several unresolved issues in the context of sperm DNA fragmentation (SDF) (1). Indeed, we appreciate and agree with his comments that development of better diagnostic methodology, evaluation of true functional consequences and understanding of oocyte repair capacity are important areas of research. It is widely believed that SDF is one of the major causes of male infertility and that DNA fragmentation can be caused by a variety of factors such as infection, chemotherapy, radiotherapy, smoking, drug use, or advanced age (2). Furthermore, SDF is linked to impaired fertilization, poor embryo quality, increased spontaneous abortion rates and reduced pregnancy rates after assisted reproduction (3).

Dr. Oehninger's comments about the "limited number of studies showing that SDF levels can predict the likelihood of natural pregnancy and that higher SDF levels are associated with lower intrauterine insemination (IUI) pregnancy rates, and with lower embryo quality and pregnancy rates in the in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) scenario" are valid but deserve to be viewed in a correct perspective. Although only a few studies reported the role of SDF in natural pregnancy, they have consistently demonstrated a significant odds ratio (OR). A meta-analysis by Zini involving 3 studies and 616 couples, showed that high SDF as measured by sperm chromatin structure assay (SCSA) was associated with a failure to achieve natural pregnancy with an OR of 7.01 (4). The Danish first pregnancy planners study clearly illustrated that the time-to-pregnancy increased with sperm DNA fragmentation index (DFI) and men became infertile when the DFI exceeded 30% in an unselected population (5). The role of SDF in fertility assessment was further supported by recent data where the authors reported a sensitivity of 80.8% and specificity of 86.1% in predicting pregnancy with a cutoff of 26.1% by sperm chromatin dispersion (SCD) method (6). More importantly, the SDF testing showed a predictive value independent of conventional semen parameters (7). The effect of SDF on assisted reproductive technologies (ART) outcomes were widely reported previously and continued to be supported by upcoming data. Lower pregnancy rate with IUI was correlated with higher DFI and there was a significant difference in DFI between males with successful and unsuccessful IUI outcomes, as reported in a recent study (8). There is even more evidence signifying the deleterious effect of SDF on embryo quality. Simon *et al.* demonstrated the paternal influence of SDF on early embryonic development and implantation (9). The tremendous number of studies on the effect of SDF on IVF and ICSI outcomes were summarized in a review and meta-analysis (10,11). An analysis of a total of 8,068 treatment cycles revealed a significantly negative effect of SDF on clinical pregnancy in both IVF and ICSI (11). Despite all the current hurdles in clinical application of SDF testing, the predictive value of SDF in both natural pregnancy and ART outcomes has been consistently supported by utilizing various testing methods in different patient groups. Therefore it is critical that we should not overlook the expanding evidence on SDF testing.

Another point raised by Dr. Oehninger is that SDF tests

do not diagnose absolute numbers of DNA breaks and/or are not able to quantify the amount or type of DNA damage in sperm. We certainly agree that more researches are needed in determining the nature of DNA breaks. The identification of clinically significant DNA breaks is of paramount importance and is based on the knowledge of the type and site of a DNA break while the detailed quantification of SDF alone may be less helpful in reflecting the clinical significance. Nonetheless, the stratification of DNA damage into testicular or post-testicular events could help in our understanding of the pathophysiology and development of new treatment strategies. Moreover, neat semen was widely used in SDF studies for prediction of pregnancy, while the predictive ability of SDF in post-processed specimens is less reported (12). While reports suggesting swim-up and/or density gradient centrifugation (DGC) may be helpful in isolating sperm with less amount of SDF are available (13), the use of processed semen samples for SDF testing remains controversial. SCSA DFI level of DGC-processed sperm did not predict ART outcome in contrast to neat samples, despite the reduction in DFI to less than 30% (14). Niu *et al.* reported that the reduced sperm SCSA DFI after swim-up predicted day 3 embryo quality, but showed no association with fertilization, implantation and pregnancy rates (15). Therefore, the choice of the most appropriate sample for SDF testing warrants further research. After all, SDF testing has a role at least in neat semen, and may be potentially applicable in other samples including processed semen.

The complexity of human reproduction with involvement of numerous confounding factors from both male and female sides poses inherent difficulty in drawing a guideline. We acknowledge that well-designed randomized controlled trials providing grade A evidence are the best guide for clinical management of infertile couples. On the other hand, we have to be realistic that high level evidence in this field will probably be not available in the coming few years. Therefore, why should we stick to conventional semen analysis which is mostly based on weak evidence if subjected to stringent scientific review (16) and ignore the larger body of evidence supporting the potential use of SDF tests? We admit that the SDF tests may not perform better than semen analysis in predicting fertility potential alone, but it will surely provide complementary and unique information that is an essential component in a complete male fertility assessment. SDF test is on the right track with the current available evidence. We believe that the practice recommendations by Agarwal *et al.* (17) is one of the major steps forward in transforming SDF scientific findings into clinical practice with the current best available, though not perfect, evidence.

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Footnote

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

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