Commentary

Clinical implication of DNA fragmentation in male infertility

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Comment on: Agarwal A, Majzoub A, Esteves SC, *et al*. Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios. Transl Androl Urol 2016;5:935-50.

Submitted Nov 27, 2016. Accepted for publication Dec 08, 2016.
doi: 10.21037/tau.2017.01.07
View this article at: http://dx.doi.org/10.21037/tau.2017.01.07

Recently, sperm DNA fragmentation (SDF) has been recognized as an important marker of sperm quality that can be used as a predictive factor for fertility in men. Although some controversies exist regarding the role of SDF in infertility, the fact remains that semen from infertile men possess a higher level of SDF than fertile controls (1,2). Elevated SDF may not only contribute to higher rates of failed fertilizations and spontaneous pregnancy loss, but it can also affect assisted reproductive techniques (ART) outcomes in terms of oocyte fertilization, embryo quality, clinical pregnancy and live birth rate. However, controversy still exists regarding the association between SDF and the outcomes of intracytoplasmic sperm injection (ICSI) (3,4).

There are different techniques available for measuring SDF, the most popular of which are sperm chromatin structure assay (SCSA), terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and sperm chromatin dispersion (SCD or Halo test) (5). Common limitations in all these techniques are the high cost, technical expertise needed, lack of test standardization and agreeable fixed cut-off values which hinder their routine use for assessment of male infertility.

The current work by Agarwal and coworkers presents a schematic review of SDF and its relation to different etiological factors, together with a critical review of all tests used to detect SDF providing a reference guideline for clinical application of the controversial SDF in the field of male infertility.

Studies have proved that infertile men with varicocele have elevated SDF especially in higher clinical varicocele grades. Furthermore, other studies have confirmed that the post-varicocelectomy improvement in SDF in this group of patients is associated with improvement of other semen parameters and pregnancy rates (6). The current guidelines by Agarwal *et al*., provides a good level of evidence for using such a tool in selecting patients for varicocelectomy especially low grade varicocele with borderline semen parameters (5). Nevertheless, concluding that SDF can predict fertility in varicocele patients is limited by the fact that we are frequently encountered by patients with advanced varicocele and normal fertility status. So the presence of high SDF and clinical varicocele is not a clear detrimental evidence that the affected person is infertile suggesting that some patients may have intrinsic scavenging mechanism that overcome the effect of high DNA damage. Therefore, we believe that a clinical study should be performed to detect the difference between infertile patients with varicocele compared to age matched fertile patients with varicocele. A new cut off value for prediction of fertility in cases of varicocele may be concluded from such a study.

Unexplained infertility is a very unsatisfactory diagnosis for both couples and doctors. In this subset of patients, a high SDF may be the cause of infertility in up to 17.7% of patients despite the presence of normal semen parameters (7). Therefore, the mere use of conventional semen for evaluation of males with unexplained infertility is not enough. We agree with the authors that SDF testing in these patients will help to orchestrate the best management plan.

Further compelling reasons for testing of SDF comes from strong association with miscarriage whether following natural pregnancy or ART. Similarly, SDF negatively affects outcome of intrauterine insemination (IUI) (8,9).

A greater controversy arises when discussing the effect of SDF on IVF and ICSI. While many studies have proven that high SDF negatively affects the IVF/ICSI outcome, other studies failed to reach similar conclusions (10). The proposed recommendations by the present review have set clear guidelines for SDF testing in these cases especially in recurrent IVF/ICSI failure. However, we must approach this area with caution due to the critical role of female age in IVF/ICSI success. Oocytes have a capacity to repair DNA damage even if the injected sperm is of poor quality (11). This capacity is decreased by age therefore accentuating the effect of SDF. We believe that recommendations regarding SDF effect on IVF/ICSI should be adjusted to female age where SDF should be tested prior to the procedure in older female age.

SDF is elevated in infertile men with unhealthy life style including obesity, cigarette smoking and occupational exposure to hazardous material (12). However, there is a lack of studies denoting decrease in SDF level with adjustment of life style factors e.g., weight loss, cessation of smoking or changing the occupation. This limits the clinical significance for the role of SDF testing in such cases. Therefore, more studies should be carried out to evaluate the effect of life style modification on SDF.

The guidelines presented by the authors in the present work will definitely lead to increase in the proper use of SDF testing in the evaluation of male infertility. It will help other researchers to generate more studies addressing limitations of current studies on SDF and infertility which will lead to more refinement of use of SDF testing.

Acknowledgements

None.

Footnote

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

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Cite this article as: Arafa M, ElBardisi H. Clinical implication of DNA fragmentation in male infertility. Transl Androl Urol 2017;6(Suppl 4):S656-S657. doi: 10.21037/tau.2017.01.07

