Editorial

Future direction in sperm DNA fragmentation testing

Chak-Lam Cho[1], Ashok Agarwal[2], Ahmad Majzoub[3], Sandro C. Esteves[4]

[1]Division of Urology, Department of Surgery, Kwong Wah Hospital, Hong Kong, China; [2]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA; [3]Department of Urology, Hamad Medical Corporation, Doha, Qatar; [4]ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil

Correspondence to: Ashok Agarwal. Professor and Director, American Center for Reproductive Medicine, Cleveland Clinic, Mail Code X-11, 10681 Carnegie Avenue, Cleveland, OH 44195, USA. Email: AGARWAA@ccf.org.

Response to: Rey RA. Commentary on sperm DNA fragmentation testing clinical guideline. Transl Androl Urol 2017;6:S522-4.

Submitted Jun 03, 2017. Accepted for publication Jun 03, 2017.
doi: 10.21037/tau.2017.06.14
View this article at: http://dx.doi.org/10.21037/tau.2017.06.14

Dr. Rey, in his commentary (1), has provided us with a comprehensive summary of the practice recommendations proposed by Agarwal *et al.* (2) with additional discussion on the basic physiology of sperm DNA structure.

The pros and cons of the eight available sperm DNA fragmentation (SDF) tests were listed by the author. Dr. Rey correctly pointed out that Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) test is relatively simple, sensitive, reliable and has very low inter-observer variability. In fact, the standardization of the assay between laboratories has been established recently by a multicenter study. By using identical instruments and protocols between two laboratories at Cleveland, USA, and Basel, Switzerland, a high correlation in TUNEL results could be achieved when the same set of semen samples was independently analyzed (3). Although all SDF tests currently suffer from the common pitfall that the nature and type of DNA damage are unclear (4), numerous studies have illustrated the prognostic value of SDF tests irrespective of the testing method used (5). The evolving knowledge and continuous effort from researchers in refining SDF tests will certainly enhance the performance of these advanced sperm function tests in the near future.

The evidence-based indications of SDF testing put forward by Agarwal *et al.* was supported by Dr. Rey. In fact, the indications proposed represent the first step in promoting the clinical application of SDF tests. The use of SDF tests should not be limited by the practice recommendations. Expanded indications should apply with an understanding of the principles of the assay. We would like to further illustrate this point in the following paragraphs. The use of SDF tests in better stratification of patients in varicocele treatment and assisted reproductive technology (ART) are discussed.

Search for advanced diagnostic and assessment tests continues in view of a lack of reliable prognostic factors for varicocele repair. The decision to repair a varicocele with reference to professional society guidelines based on presence of clinical varicocele and abnormal conventional semen parameters does not predict treatment success (6). Recent evidence clearly supported the association between varicocele and SDF, and the negative implication of SDF on pregnancy outcomes is increasingly being unmasked (7). The effect of varicocelectomy in ameliorating SDF has also been demonstrated (8-10). Therefore, the potential role of SDF tests in identification of suitable surgery candidates is valid. It is suggested in the practice recommendations that SDF is recommended in patients with grade 2/3 varicocele with normal conventional semen parameters and in patients with grade 1 varicocele with borderline/abnormal conventional semen parameters (2). The essence is to introduce the use of SDF tests in providing additional information in case of ambiguity based on clinical grading of varicocele and conventional semen parameters. We believe that the statement based on current best evidence is a relatively conservative one. With ever expanding evidence on the clinical use of SDF in clinical practice, we foresee the incorporation of SDF test results, together with other factors, as one of the essential predictors of post-varicocelectomy outcome in a prognostic model/nomogram.

In patients with unexplained infertility and total motile sperm count of over 5 million, intrauterine insemination

(IUI) is often the treatment of choice. Strong correlation between sperm DNA fragmentation index (DFI) greater than 30% by Sperm Chromatin Structure Assay (SCSA) and decreased pregnancy and delivery rates after IUI has been demonstrated with an odds ratio (OR) of 9.9 (11). In another study, insemination of >12% TUNEL-positive spermatozoa resulted in no pregnancy (12). The correlation between high SDF and poor IUI outcome is further supported by a recent study which reported a DFI >27%, measured by SCSA, to have negative impact on IUI pregnancy rate (13). On the other hand, the relationship between SDF and pregnancy rates after *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) is significant but modest with OR of around 1.5 (4). As a result, IVF/ICSI is often considered as the next step for patients with repeated IUI failures. In view of the appealing predictive value of SDF on IUI outcomes, the introduction of the tests prior to IUI cycles is rational. The SDF test may better stratify infertile couples to ART with better success rates. Despite the seemingly less complicated and less costly IUI cycles, the possible value of SDF tests in preventing failed IUI cycles should not be overlooked. Wider use of non-invasive SDF tests before IUI cycles may prove to be safer, more time-saving and cost-effective than the "trial and error" approach by using multiple IUI cycles.

The practice recommendations by Agarwal *et al.* (2), though important, is just the initial step in moving SDF tests from bench to clinic and should not be regarded as the ultimate goal. The current recommendations serve as a solid evidence-based foundation for future development and we are looking forward to upcoming evidence in expanding the scope of SDF testing in the management of infertile couples.

Acknowledgements

None.

Footnote

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

References

1. Rey RA. Commentary on sperm DNA fragmentation testing clinical guideline. Transl Androl Urol 2017;6:S522-4.
2. 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.
3. Ribeiro S, Sharma R, Gupta S, et al. Inter- and intra-laboratory standardization of TUNEL assay for assessment of sperm DNA fragmentation. Andrology 2017;5:477-85.
4. Agarwal A, Cho CL, Esteves SC. Should we evaluate and treat sperm DNA fragmentation? Curr Opin Obstet Gynecol 2016;28:164-71.
5. Gosalvez J, Lopez-Fernandez C, Fernandez JL, et al. Unpacking the mysteries of sperm DNA fragmentation ten frequently asked questions. J Reprod Biotechnol Fertil 2015;4:1-16.
6. Samplaski MK, Jarvi KA. Prognostic factors for a favourable outcome after varicocele repair in adolescents and adults. Asian J Androl 2016;18:217-21.
7. Cho CL, Esteves SC, Agarwal A. Novel insights into the pathophysiology of varicocele and its association with reactive oxygen species and sperm DNA fragmentation. Asian J Androl 2016;18:186-93.
8. Li F, Yamaguchi K, Okada K, et al. SIgnificant improvement of sperm DNA quality after microsurgical repair of varicocele. Syst Biol Reprod Med 2012;58:274-7.
9. Baker K, McGill J, Sharma R, et al. Pregnancy after varicocelectomy: impact of postoperative motility and SFI. Urology 2013;81:760-6.
10. Kadioglu TC, Aliyev E, Celtik M. Microscopic varicocelectomy significantly decreases the sperm DNA fragmentation index in patients with infertility. Biomed Res Int 2014;2014:695713.
11. Bungum M, Humaidan P, Axmon A, et al. Sperm DNA integrity assessment in prediction of assisted reproduction technology outcome. Hum Reprod 2007;22:174-9.
12. Duran EH, Morshedi M, Taylor S, et al. Sperm DNA quality predicts intrauterine insemination outcome: a prospective cohort study. Hum Reprod 2002;17:3122-8.
13. Rilcheva VS, Ayvazova NP, Ilieva LO, et al. Sperm DNA integrity test and assisted reproductive technology (ART) outcome. J Biomed Clin Res 2016;9:21-9.

Cite this article as: Cho CL, Agarwal A, Majzoub A, Esteves SC. Future direction in sperm DNA fragmentation testing. Transl Androl Urol 2017;6(Suppl 4):S525-S526. doi: 10.21037/tau.2017.06.14

