Editorial

All-round approach in diagnosis

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

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

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: Veeramachaneni DN. Utility of testing sperm DNA fragmentation: an all-in-one diagnostic tool to address a multi-pronged clinical problem. Transl Androl Urol 2017;6:S462-4.

Submitted Apr 13, 2017. Accepted for publication Apr 13, 2017.
doi: 10.21037/tau.2017.04.22
View this article at: http://dx.doi.org/10.21037/tau.2017.04.22

Dr. Veeramachaneni (1) in response to the practice recommendations by Agarwal *et al*. (2) reminded the importance of interacting multiple factors on reproductive system. Indeed, it is of paramount importance to rule out reversible factors (such as genital tract infection and exposure to environmental toxicants) during the assessment and management of infertile patients. In contrary to the notion of one-man one-disease in traditional teaching, multiple intercalating factors are often present in a couple investigated for infertility (3). This is one of the reasons for the standardization of semen sample collection before any test in order to minimize the impact of confounding factors (4). These include possible exposure to heat stress, drugs and environmental toxins which should be ruled out in the history taking before clinical tests. Symptoms or microscopic features (e.g., leukocytospermia) suggestive of genitourinary tract infection warrants further investigation and correction (5).

Dr. Veeramachaneni enlightened the reader on his extensive experience in utilizing light and transmission electron microscopic evaluation on semen samples (1). We wish to discuss and comment on this important technique. The principle of transmission electron microscopy (TEM) addresses the deficiency of routine light microscopy in characterization of subtle lesions in spermatozoal organelles and cellular debris in the semen. Indeed, TEM has been used extensively in studies of immotile human spermatozoa (6). TEM is potentially useful for investigation of severely asthenozoospermic patients. The stratification of patients by different TEM features, i.e., dysplasia of the fibrous sheath or non-specific flagellar anomaly, points to different etiologies and prognosis in pregnancy outcome (7). It is, therefore, postulated that this approach allows assessment of seminal components and characterization of pathologic conditions in the genital tract (8). Although structure and function may correlate to a certain extent, not all structurally normal spermatozoa have normal function and vice versa. Experience with sperm DNA fragmentation (SDF) testing has shown that sperm with high DNA fragmentation can have normal motility and morphology (9). In addition, intra-individual variations is a major concern during assessment of any sort of semen characteristics/parameters. Similarly, the inter-observer variations in the results of TEM may be significant since the technique requires high level of expertise in cytological assessment. The method of TEM may have the same drawback as semen analysis in variations between laboratories and in an individual over the course of time (10). On the other hand, the validity of a single Sperm Chromatin Structure Assay (SCSA) analysis has been shown to have a high predictive value for assessment of fertility *in vivo* (11). As suggested by Dr. Veeramachaneni, cytological technique may possibly characterize the pattern of SDF which may point to different etiologies (1). However, a particular pattern of ultrastructural changes in semen may more likely point to a common mechanism rather than revealing pathognomonic features specifically suggestive of a diagnosis. Further studies are required to correlate

© Translational Andrology and Urology. All rights reserved.

cytological features under TEM and underlying etiology. The presence of SDF as suggested by ultrastructural change may not imply the presence of pathological conditions since a certain level of SDF is present in normal fertile individuals (12). Although visualization of pattern of SDF was suggested by the author as a potential diagnostic tool, more data is needed in determining its exact role.

The technique of TEM has been studied mainly in animal models (13). However, its utility in clinical practice must be supported by human data. Many of the studies were conducted with a relatively short duration of single-agent exposure to toxin (8). The result may not be applicable to clinical practice in human when chronic low-dose exposure to multiple environmental toxins is commonplace. The degree of implication of ultrastructural alterations in sperm and semen is unknown. Further studies in correlating TEM findings with reproductive outcomes, e.g., fertilization rate and embryo quality, will be useful. Nonetheless, TEM study on semen possibly provides a non-invasive alternative to assessment of infertile male. The ability to assess desquamated germ cells, denuded Sertoli cells and epithelial fragments from excurrent ducts and accessory glands is unique among currently available technologies. Preliminary data demonstrating the ability to diagnose intratubular germ cell neoplasia in a non-invasive manner is attractive since there is a relationship between infertility and testicular malignancy (14).

We realize that every clinical test has its strengths and weaknesses and there is room for refinement of both SDF testing and TEM study alike. The encouraging preliminary findings of laboratory tests in the bench require verification in human studies to elucidate their role in clinics. In the context of complex reproductive system, a single test with clear cut-off values is probably not available (15). We trust that a comprehensive panel of analyses, including both structural and functional assays, are needed for the full assessment of patients.

Acknowledgements

None.

Footnote

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

References

1. Veeramachaneni DN. Utility of testing sperm DNA fragmentation: an all-in-one diagnostic tool to address a multi-pronged clinical problem. Transl Androl Urol 2017;6:S462-4.
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 World Health Organization. WHO Manuel for the standardised investigation and diagnosis of the infertile couple. Cambridge: Cambridge University Press, 2000.
4 World Health Organization. WHO Manuel for the examination and processing of human semen. 5th edition. Cambridge: Cambridge University Press, 2010.
5 The optimal evaluation of the infertile male: AUA best practice statement. Available online: https://www.auanet.org/guidelines/male-infertility-optimal-evaluation-(reviewed-and-validity-confirmed-2011)
6 Zamboni L. The ultrastructural pathology of the spermatozoon as a cause of infertility: the role of electron microscopy in the evaluation of semen quality. Fertil Steril 1987;48:711-34.
7 Chemes HE, Olmedo SB, Carrere C, et al. Ultrastructural pathology of the sperm flagellum: association between flagellar pathology and fertility prognosis in severely asthenozoospermic men. Hum Reprod 1998;13:2521-6.
8 Veeramachaneni DN. Ultrastructural evaluation of semen to assess effects of exposure to toxicants. Toxicol Pathol 2012;40:382-90.
9 Sakkas D, Urner F, Bizzaro D, et al. Sperm nuclear DNA damage and altered chromatin structure: effect on fertilization and embryo development. Hum Reprod 1998;13:11-9.
10 Esteves SC, Hamada A, Kondray V, et al. What every gynecologist should know about male infertility: an update. Arch Gynecol Obstet 2012;286:217-29.
11 Oleszczuk K, Giwercman A, Bungum M. Intra-individual variation of the sperm chromatin structure assay DNA fragmentation index in men from infertile couples. Hum Reprod 2011;26:3244-8.
12 Saleh RA, Agarwal A, Nelson DR, et al. Increased sperm nuclear DNA damage in normozoospermic infertile men: a prospective study. Fertil Steril 2002;78:313-8.
13 Veeramachaneni DN, Moeller CL, Sawyer HR. Sperm morphology in stallions: ultrastructure as a functional

© Translational Andrology and Urology. All rights reserved.

and diagnostic tool. Vet Clin North Am Equine Pract 2006;22:683-92.
14 Jacobsen R, Bostofte E, Engholm G, et al. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. BMJ 2000;321:789-92.
15 Agarwal A, Cho CL, Esteves SC. Should we evaluate and treat sperm DNA fragmentation? Curr Opin Obstet Gynecol 2016;28:164-71.

Cite this article as: Agarwal A, Cho CL, Esteves SC, Majzoub A. All-round approach in diagnosis. Transl Androl Urol 2017;6(Suppl 4):S465-S467. doi: 10.21037/tau.2017.04.22

© Translational Andrology and Urology. All rights reserved.