

# It is high time for clinical application of sperm DNA fragmentation testing

Chak-Lam Cho<sup>1</sup>, Ashok Agarwal<sup>2</sup>, Ahmad Majzoub<sup>3</sup>, Sandro C. Esteves<sup>4</sup>

<sup>1</sup>Division of Urology, Department of Surgery, Kwong Wah Hospital, Hong Kong, China; <sup>2</sup>American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA; <sup>3</sup>Department of Urology, Hamad Medical Corporation, Doha, Qatar; <sup>4</sup>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.

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We read with interest the commentary by Drs. Basar and Kahraman (1). The authors provide a comprehensive review of sperm DNA fragmentation (SDF) from etiologies and assisted reproduction outcomes to treatment strategies. We wish to further elaborate the discussion on the use of SDF testing in managing varicocele.

Varicoceles can be found in 35–50% and up to 69–81% of men with primary infertility and secondary infertility, respectively (2,3). It is considered the most commonly identifiable and surgically correctable male infertility factor. However, controversies continue to plague the studies designed to answer the clinical question related to the effect of varicocele repair on improvement in semen parameters and pregnancy rates. Results from systematic review and meta-analyses were divided and have led to more confusion (4–6). These conflicting results are the main contributing factor to the vague and inconsistent guidelines on the diagnosis and treatment of varicoceles from various professional societies including the American Society for Reproductive Medicine (ASRM) (7), American Urological Association (AUA) (8) and European Urological Association (EAU) (9). Although most professional society guidelines agree on varicocele repair in patients with clinical varicocele and impaired semen parameters, however, they fail to settle the debate of varicocele treatment.

Despite the fact that repair of subclinical varicocele is generally not recommended by guidelines and meta-

analyses, there are reports suggesting potential role of treatment for subclinical varicocele (10). The possible benefit of simultaneous repair of subclinical varicocele with a contralateral clinical varicocele has also been recognized (11,12). On the other hand, repair of clinical varicocele does not necessarily lead to desirable outcome. Recent data support an association between grade of clinical varicocele and improvement in semen parameters after repair. Several studies consistently reported a significant difference in semen parameter outcomes after repair of high- vs. low-grade varicocele. The total motile sperm count after varicocelectomy improved by 128% in men with grade 3 varicoceles compared with a mere 21% and 27% in men with grade 2 and 1 varicoceles respectively (13). Takahara *et al.* also demonstrated the relationship between clinical grading of varicocele and post-varicocelectomy increase in sperm density. There was an improvement in sperm density of  $38 (\pm 36) \times 10^6/\text{mL}$  for large varicocele compared to  $3 (\pm 18) \times 10^6/\text{mL}$  improvement in small varicocele (14). As a result, the dichotomous classification of clinical and subclinical varicocele in decisions to proceed with surgical repair may be flawed. Similarly, the use of abnormal semen parameters in treatment decision may not be ideal. The revised lower reference limits for semen analyses by the World Health Organization (WHO) in 2010 (15) re-categorized previously abnormal men as normal and may leave this

group of men untreated (16,17). Therefore, supplementary diagnostic tools including sperm function tests are needed in refining the assessment of varicocele patients.

The association between SDF and varicocele, and the effect of varicocelectomy on SDF provide proof in supporting the potential role of SDF testing to better identify surgery candidates (18). The use of SDF testing is further supported by an understanding of the pathophysiological relationship among varicocele, oxidative stress and SDF (19). Drs. Basar and Kahraman pointed out that impaired seminal parameters regardless of varicocele grade already fulfill the indication to operate according to the current international guidelines, which is correct (1). However, we wish to point out the shortcoming of the current guidelines. The use of physical examination finding and conventional semen parameters in treatment decision of varicocele patients is far from perfect. Indeed, based on the current best evidence, Agarwal *et al.* did not recommend the routine use of SDF testing in all patients with varicocele but highlighted the value of the test in patients with high grade varicocele with normal semen parameters and low grade varicocele with borderline/abnormal semen parameters (20). We believe that the additional information on sperm function offered by SDF testing will allow selection of a subset of patients who have compromised sperm function and yet normal conventional semen parameters.

The more widespread use of SDF testing in patients with varicocele and incorporation of the test into various professional society guidelines require more supporting evidence in the literature. However, the shortcoming of the current practice should not be overlooked. We believe that SDF testing is an important tool in completing the assessment of infertile men. The practice recommendations proposed by Agarwal *et al.* is only the first step forward to bridge the gap between research and clinical practice in promoting SDF testing. There is a long way to go before we can fully unmask the mysteries of varicocele. We hope the practice recommendations will serve as a valuable reference to researchers and clinicians alike and a stimulus to provoke further discussion. Better understanding of male infertility and refinement of SDF testing would not be possible without the broad support of fertility specialists from around the world.

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### Footnote

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

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