

# Sperm DNA fragmentation: a key player in decision making

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We read, with great interest, the commentary written by Wayland Hsiao on the “Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios” (1). The author acknowledges sperm DNA fragmentation as an important addition to conventional methods for assessment of sperm quality highlighting the need for practice guidelines to describe its utility in different clinical scenarios. The author has critically appraised the utility of SDF in varicocele, as a tool to indicate testicular sperm retrieval in patients with recurrent pregnancy loss after intracytoplasmic sperm injection (ICSI) and in patients with lifestyle risk factors. His comments which are probably echoed by many, are indeed legitimate warranting a response aimed to further clarify the appropriate application of SDF for male fertility evaluation.

The author’s notion that SDF may be considered as an independent parameter of sperm quality in varicocele patients’ needs further discussion. SDF levels have been negatively correlated with sperm concentration, motility and normal morphology in infertile men regardless of the varicocele status (2). However, it seems true that patients with clinical varicocele and normal semen parameters exhibit significantly higher SDF levels than patients without varicocele (3). Moreover, it has been reported that patients with varicocele have a higher proportion of sperm with ‘massive’ DNA fragmentation, so-called ‘degraded sperm’, than infertile men without varicocele (4). The authors of the study mentioned above have postulated that the over-representation of sperm with degraded DNA in the semen is indicative of varicocele. The controversy surrounding the effects of varicocele on male fertility together with the

fact that conception rather than improvement in sperm quality is the real sought outcome after varicocelectomy prompted the use of SDF testing in this patient population. Evidence suggests that significant reductions in SDF occur after varicocelectomy, but more importantly, such changes are associated with a higher likelihood of conception (5,6). These findings, coupled with the independent existence of SDF in varicocele patients highlights the clinical utility of SDF testing when selecting patients for surgery (1).

The author advised us to be cautious in patients with severe SDF, as varicocelectomy may not be enough to revert sperm DNA integrity to normal levels. He cited the prospective clinical study by Smit *et al.* which evaluated SDF levels and pregnancy outcomes of 49 men with clinical varicocele who underwent varicocelectomy (7). These authors observed significantly higher SDF levels in patients who failed to conceive after surgery. While we do agree with Dr. Hsiao that in cases with severe SDF, varicocele may not be entirely responsible and hence proper patient counselling before surgery is advised, we actually find the results of Smit *et al.* to be fully in favor of using SDF during the evaluation of patients with clinical varicocele. In their study, the authors reported a significant decrease in SDF (measured with sperm chromatin structure assay) after surgery from 35.2% to 30.2% (P=0.019). Moreover, out of the included couples in the study, 37% conceived naturally and 24% achieved pregnancy with an assisted reproductive technique (ART) after varicocelectomy. More importantly, SDF levels were significantly lower in those who achieved pregnancy whether naturally or through ART. The authors concluded that “*After varicocelectomy sperm parameters significantly improved and sperm DNA fragmentation was*

*significantly decreased. Low DNA fragmentation index values are associated with a higher pregnancy rate”.*

Compelling evidence extracted from systemic reviews and meta-analyses suggest that SDF affects the overall outcome of ICSI as a direct relationship exists between the level of SDF and the likelihood of pregnancy loss after ICSI (8-10). Against all our efforts, attempts at normalizing SDF levels before ICSI may be unsuccessful in a good number of patients. Hence, search for novel methods that can ultimately improve the live birth rate after ICSI is entirely justified. Most DNA damage occurs during the epididymal transit of sperm as evidenced by several reports observing significantly higher SDF in ejaculated sperm than testicular sperm (11-13). As such, the use of testicular sperm for ICSI in patients with high SDF has been investigated in a few studies with promising results (11,13,14). In a recent study by our group (15), 37 couples who had history of recurrent pregnancy loss after ICSI and male partners with high levels of SDF successively underwent an ICSI trial with testicular sperm. The outcome of the testicular sperm ICSI trial was compared with the prior ejaculated sperm ICSI trial. Seventeen couples (45.9%) had a live birth after testicular sperm ICSI compared with 3 couples (8.1%) after ejaculated sperm ICSI ( $P<0.001$ ). While we do agree with the author that more research is needed in this area, the growing evidence justifies counselling patients with high SDF and recurrent pregnancy loss after ICSI towards using testicular sperm instead of ejaculated sperm for the subsequent trial. This does not mean that we are suggesting all men to a sperm retrieval procedure, as Dr. Hsiao noted; instead, we believe that such an option can be offered for patients given the lower incidence of pregnancy loss when testicular sperm are used in ICSI.

We acknowledge the author's keenness for counselling his patients towards adopting a healthier lifestyle and we do believe that this is the making of a successful physician. Moreover, we also agree that a laboratory test such as SDF is surely not a prerequisite for counselling. In a recent meta-analytic study, the negative effects of smoking have been confirmed using conventional semen analysis (16). However, smoking cessation is generally not easy to accomplish and only about 4–6% of smokers attempting to quit actually succeed (17). SDF can be looked at as a simple, non-invasive laboratory test that provides solid evidence on the hazards of smoking on the patients' health in general and their fertility in particular. In this sense it may motivate patients to adapt a healthier lifestyle. Furthermore, it can also be used as a monitoring tool to follow patients'

compliance with the healthy lifestyle program.

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## Footnote

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

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