

# Expanding treatment paradigm of high sperm DNA fragmentation

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*Response to:* Tatem A, Brannigan RE. The role for sperm DNA damage testing in 2017. *Transl Androl Urol* 2017;6:S448-9.

Submitted Mar 12, 2017. Accepted for publication Mar 12, 2017.

doi: 10.21037/tau.2017.03.72

View this article at: <http://dx.doi.org/10.21037/tau.2017.03.72>

We appreciate the commentary by Drs. Tatem and Brannigan (1) that largely support the practice recommendations proposed by Agarwal *et al.* (2). We would like to further elaborate on two points in the commentary: (I) the correlation between SDF and varicocele, and (II) treatment for abnormal SDF. We think the discussion may help provide more in depth information to the readers.

Varicocele is the most common cause of primary and secondary infertility in men (3,4). The benefit of varicocelectomy has been proven with 60–80% improvement in semen parameters and 20–60% improvement of natural pregnancy in couples (5). Nevertheless, only 20% of adult men with varicocele have difficulties conceiving (6), which means treatment may not be required for all patients. Selection of patients who will benefit from surgical intervention remains challenging and the use of conventional semen parameters as the laboratory indicator for treatment decision is flawed (7). A number of studies have examined the association between varicocele and SDF. Zini *et al.* reported that both fertile and infertile men with varicocele tend to have higher SDF than controls, thus suggesting that varicocele is associated with DNA damage even when fertility has not been compromised (8). The relationship between varicocele and SDF is mediated via oxidative stress and the mechanism has been reviewed (9). The effect of varicocelectomy on improving sperm DNA integrity has been reported in some studies (10,11). A meta-analysis of six studies including 177 patients evaluated the effect of varicocelectomy on SDF. The authors reported that varicocelectomy improves sperm DNA integrity with a mean difference of 3.37% (12). The low magnitude of

effect size may be contributed by the heterogeneous study population and study design and further research is needed to elucidate the clinical significance of varicocelectomy on SDF. The current evidence suggest that the SDF test may be a potentially useful tool in identifying appropriate patients for varicocelectomy in view of the correlation of SDF and fertility in patients with varicocele, and the reversible nature of SDF with treatment. SDF test may be particularly useful in cases of infertile normozoospermic men with varicocele. Treatment may benefit patients with poor sperm DNA integrity as revealed by SDF test despite normal semen parameters (13). The test result may also affect management of adolescent varicocele by objectively demonstrating testicular dysfunction which may predict possible progression to infertility. Studies showed that sperm nuclear DNA fragmentation was increased in adolescent with varicocele despite the lack of difference in semen parameters compared to non varicocele group (14) and the beneficial effect of varicocelectomy in adolescents was also suggested by increased sperm DNA integrity and mitochondrial activity after operation (15).

Treatment of high SDF when no specific identifiable etiology, as opposed to the case of varicocele, is less well defined and is a major reason why professional societies (ASRM and AUA) guidelines do not endorse the routine use of SDF analysis (16,17). However, emerging clinical data in recent years may offer changes to this outlook. There are several proposed interventions aimed at decreasing the percentage of sperm with DNA fragmentation (18). Sperm preparation techniques including swim-up and/or density gradient centrifugation can significantly reduce SDF (19).

However, no clinical benefit has been demonstrated (20). On the other hand, sperm selection technique and use of testicular sperm during ICSI seems more promising. A recent study by Bradley *et al.* reported the effectiveness of intervention in patients with high SDF. The fertilization rate, fetal heart pregnancy rate and live birth rate showed significant improvement after interventions including physiological intracytoplasmic sperm injection (PICSI), intracytoplasmic morphologically selected sperm injection (IMSI) and testicular sperm extraction/aspiration (TESE/TESEA). The clinical outcome of high SDF patients after intervention were similar to low SDF group (21). The use of testicular sperm is further solicited by Esteves *et al.* who demonstrated a higher clinical pregnancy rate (51.9% *vs.* 40.2%), a lower miscarriage rate (10.0% *vs.* 34.3%) and higher birth rate (46.7% *vs.* 26.4%) in association with significantly lower SDF in testicular sperm compared to ejaculated sperm (8.3% *vs.* 40.7%) (22).

We envision a timely review and revision of the guidelines by various societies as new evidence has emerged and more is being added to the literature (23). Further refinement of SDF analysis will surely bring the test into the armamentarium of every fertility specialists.

## Acknowledgements

None.

## Footnote

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

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**Cite this article as:** Agarwal A, Cho CL, Majzoub A, Esteves S. Expanding treatment paradigm of high sperm DNA fragmentation. *Transl Androl Urol* 2017;6(Suppl 4):S450-S452. doi: 10.21037/tau.2017.03.72

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