

Sperm DNA fragmentation testing: proceed with care

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Comment on: 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.

Submitted Feb 06, 2017. Accepted for publication Mar 16, 2017.

doi: 10.21037/tau.2017.03.75

View this article at: <http://dx.doi.org/10.21037/tau.2017.03.75>

The authors should be commended for their thorough review of DNA fragmentation and the clinical indications for testing. The basic science review of DNA fragmentation, oxidative stress, and its association with male infertility is detailed yet concise. The authors also present clinical scenarios to better illustrate the current role of evaluating sperm DNA fragmentation (SDF) in the infertility specialist's armamentarium, and describe very convincing theoretical arguments for the potential importance of SDF. However, the clinical role of SDF in the evaluation of men with male factor infertility remains unclear, and several recommendations made in this article do not yet have sufficient clinical data to support its routine use.

Clinical scenario #1: clinical varicoceles

According to the AUA Best Practices on Varicoceles, varicocele repair should be limited to male patients complaining of infertility with both palpable varicoceles and abnormal semen parameters or sperm function tests. Varicocele treatment is not indicated in patients with normal semen quality (1). However, the authors state that men with large varicoceles but normal semen parameters should be offered SDF testing.

If the authors support obtaining DNA Fragmentation in patients with varicoceles but normal semen parameters, then there must be evidence that improvements in SDF alone can improve pregnancy outcomes after surgical correction. To date, there are no such studies evaluating this patient population. Further, a prospective study by Nasr-Esfahani *et al.* looking at 162 patients with varicoceles found

a significant improvement in SDF after varicocelectomy. However, they found no difference in SDF levels between patients who achieved pregnancy and those that did not achieve pregnancy after varicocelectomy (2).

Additionally, the authors acknowledge there is a lack of evidence supporting treating patients with low grade varicoceles and elevated SDF. In order to justify the routine use of SDF in patients with borderline normal semen parameters and low grade varicoceles, there would need to be evidence that either SDF was a predictive factor for improvement of semen parameters or for pregnancy outcomes in these patients. This has not yet been established.

Lastly, the clinical usefulness of SDF in the routine workup for infertile men with varicoceles is still unclear. One important question remains: How many patients with varicoceles have an elevated SDF and how many of these elevated SDF levels resolve to normal levels after varicocelectomy? To date, previous literature only describes mean differences in SDF pre- and post-surgery, and do not describe tangible improvements such as resolution of elevated SDF. According to literature described in this review, an elevated SDF >30% is associated with significantly decreased spontaneous pregnancy rates (3). Future studies evaluating the clinical relevance of SDF should aim to identify what percentage of patients have significant improvements in their SDF that cross this threshold. Until more robust data are available, we cannot advocate varicocele repair for elevated SDF levels alone, and therefore we cannot advocate routinely obtaining SDF in men with varicoceles but otherwise normal semen parameters.

Scenario #2: unexplained infertility/recurrent pregnancy loss/IUI failure

In addition to recommending treating varicoceles based on SDF findings, the authors also recommend utilizing SDF during workup for couples with unexplained infertility, recurrent pregnancy loss, or those considering IUI. However, the clinical usefulness of SDF in these patients remains unclear. The authors provide a review of literature involving patients with unexplained pregnancy, which have demonstrated a correlation between unexplained infertility and elevated SDF. However, the two studies cited utilize different assays for SDF and are inconsistent in their definition of elevated SDF levels (4,5). The authors then describe published data on correlations between recurrent pregnancy loss and SDF, which have demonstrated a difference in average SDF between control population *vs.* population with recurrent pregnancy loss (6). Lastly, the authors describe the correlation between IUI success and DNA fragmentation, describing a significant difference in average DNA fragmentation between couples who achieve IUI success *vs.* those with failed IUI cycles (7,8).

The authors state that based on these data, they would recommend obtaining SDF in couples with unexplained infertility, recurrent pregnancy loss and those considering IUI. However, while the previously mentioned data shows a correlation of elevated SDF and IUI outcomes/recurrent pregnancy loss/unexplained infertility, there is no published data looking at the usefulness of screening for elevated SDF in these couples. Some important clinical points need to be addressed in these patient cohorts, such as at what level SDF would be considered “elevated” in these couples? How would you decide which couples should have SDF levels evaluated: after 2nd *vs.* 3rd pregnancy loss? How would you counsel a couple with recurrent pregnancy loss and elevated SDF? Further, a cost-analysis evaluation would be an important step towards proving the clinical role of SDF in these patients. Without more robust data regarding the clinical utility of SDF, we cannot advocate the use of routine SDF screening in this large patient population.

Clinical scenario #3: IVF and/or ICSI failure

When describing the role of SDF in caring for patients undergoing IVF/ICSI, the authors acknowledge further research is needed prior to making concrete recommendations, but go on to state that SDF testing can provide prognostic information in couples undergoing

IVF. To support this argument, the authors describe studies that have shown that elevated DNA fragmentation is associated with decreased IVF pregnancy rates. However, when comparing IVF to ICSI outcomes, the only outcomes described are pregnancy rates, and not live-birth rates. This significantly limits the utility of this data in recommending IVF *vs.* ICSI.

To address this limitation in the literature, the authors cite data that supports utilization of testicular sperm (TS) in men with elevated SDF, which suggest benefit of ICSI over conventional IVF in men with elevated SDF. According to two studies referenced in this article, men with elevated SDF who underwent ICSI using TS had higher live-birth rates compared to similar men who underwent ICSI using ejaculated sperm (9,10).

While the authors argue for the potential benefit for evaluating SDF in patients undergoing IVF, there remains a scarcity of clinical data supporting its routine use in this patient population. Important clinical questions that have not yet been addressed include determining which patients should be offered TS/ICSI: should only those with elevated SDF/male factor alone or both male and female factor? For patients undergoing IVF, what should be the cut off for SDF for recommending TS/ICSI instead of IVF? For more robust data, randomized controlled trials evaluating these clinical questions would be required. Until this data is demonstrated, we cannot make any concrete recommendations on screening SDF for couples undergoing ART.

Clinical scenario #4: lifestyle risk factors for infertility

The negative impact of smoking on semen parameters has been well established. As the authors commented, recent evidence has shown smoking to have detrimental effect on spermatozoa fertilizing capacity (11), and to be associated with increased risk for infertility. According to a recent cross-sectional study by Yang *et al.* (12), smoking men are more likely to suffer from infertility than nonsmokers, with OR of 1.58 (95% CI: 1.26–1.99).

The authors make a clear argument linking lifestyle risk factors, such as occupational exposures and smoking, to elevated SDF. The authors’ recommendation to utilize SDF testing to reinforce the importance of lifestyle modification is reasonable for patients who seem resistant to more generalized recommendations. However, as the authors have previously described, currently there is insufficient

evidence that interventions such as antioxidant therapy or lifestyle modification will result in resolution of DNA fragmentation, or improve fertility outcomes. Therefore, there is insufficient evidence to support obtaining DNA fragmentation to monitor patient's response to intervention.

In summary, the authors should be commended on writing a thorough and insightful review on the latest published literature on SDF. However, many of the recommendations made in this article do not yet have sufficient evidence accrued to justify routine use of SDF screening as part of the male factor fertility evaluation. More clinical based data is required before such concrete recommendations can be supported. Until then, SDF remains an important emerging technology whose role in the clinic is not yet entirely elucidated.

Acknowledgements

None.

Footnote

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

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Cite this article as: Johnson D, Sandlow J. Sperm DNA fragmentation testing: proceed with care. *Transl Androl Urol* 2017;6(Suppl 4):S425-S427. doi: 10.21037/tau.2017.03.75