Editorial

Sperm DNA fragmentation: a rationale for its clinical utility

Ahmad Majzoub[1], Ashok Agarwal[2], Sandro C. Esteves[3]

[1]Department of Urology, Hamad Medical Corporation, Doha, Qatar; [2]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA; [3]ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil

Correspondence to: Ahmad Majzoub. Department of Urology, Hamad Medical Corporation, Doha, Qatar Po Box 3050. Email: dr.amajzoub@gmail.com.

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We read with great interest the commentary written by Akanksha Mehta on the "*Clinical utility of sperm DNA fragmentation testing*: *practice recommendations based on clinical scenarios*" by Agarwal *et al.* (1). The author acknowledges the impact of sperm DNA fragmentation (SDF) on male fertility potential; however, she highlights important obstacles that remain to be considered during the utility of SDF testing in clinical practice such as: absence of cutoff values, cost of the test and the lack of solid evidence recommending the routine use of SDF.

SDF has been proposed as a supplementary tool that can be utilized to enhance the predictive value of conventional semen analysis during male fertility evaluation (2). Semen analysis, whilst a valuable test for fertility evaluation, is a poor predictor of conception. There is currently sufficient evidence to state that SDF is significantly associated with abnormal semen parameters and poor fertility outcome both after natural and assisted reproduction (ART) (1,3,4). During her discussion of the validity and predictive value of SDF testing, Dr. Mehta stated "*that there are no validated cut-off points for SDF that can effectively predict fertility*", and cited a SDFs sensitivity of as low as 25% and 40% in predicting pregnancy after intrauterine insemination (IUI) and *in vitro* fertilization (IVF), respectively (5,6). Finally, she supported the recommendation of the American Society for Reproductive Medicine (ASRM) which disapproves the routine use of SDF during male fertility evaluation (7). We refute these statements as they are based on rather outdated studies published almost 10 years ago (5,8). A considerable body of evidence has been published in recent years with studies aimed to achieve improved test validation and predictive power. A simple PubMed search using the word "sperm DNA fragmentation" reveals that a little more than 600 articles were added to medical literature since 2013, the date when the ASRM guideline on the utility of SDF was published (7). Recently, Chenlo *et al.* have reported that SDF, using TUNEL, is a valid independent test of fertility having a sensitivity and specificity of 85% and 89%, respectively for predicting pregnancy (9). A specificity of 91.6% has also been reported in a study by Sharma *et al.* who compared SDF values using TUNEL between 95 controls and 261 infertile men concluding that SDF is a reproducible and reliable method for fertility evaluation (10). As for its use in ART, López *et al.* (11) compared the diagnostic usefulness of SDF, measured with sperm chromatin dispersion, to high magnification tests for predicting IVF and ICSI outcomes. In a cohort of 152 infertile couples the authors reported that SDF was a better predictor of pregnancy than the degree of vacuolization assessed with high magnification where a SDF cutoff value of 25.5% had a sensitivity of 86.2% and a negative predictive value of 72.7% (P=0.02) in predicting successful IVF/ICSI treatment. Another recent study by Rilcheva *et al.* (12) utilized sperm chromatin structure assay to investigate the influence of SDF on the pregnancy outcome of 531 couples undergoing autologous ICSI (n=416), donation ICSI (n=39) and IUI (n=71). Using a cutoff value of 27%, the authors reported a statistically significant negative correlation between SDF and pregnancy outcome with IUI (χ^2=6.87; P<0.05), and a positive correlation between SDF and pregnancy loss after IUI (*t*-test =1.58; P<0.05) and ICSI (OR =5.65; 95% CI: 4.32–7.11; P<0.05). Finally, the authors concluded that infertile men should be evaluated with SDF in addition to routine semen analysis suggesting that when the result exceeds 27%, patients should be offered ICSI at an earlier stage.

The availability of several technical methods and cut-off values for SDF measurement may still hinder its routine use in clinical practice. However, it is sound to state that with the continued use of SDF testing, meaningful refinements

of its methods and diagnostic thresholds will be achieved. One study has raised this issue after examining the predictive power of different cutoff values of SDF assessed with SCD in patients undergoing IUI, concluding that each center should evaluate the type of test it uses to detect SDF and determine its own threshold values (13). Cost remains an important factor limiting the routine use of SDF. However, it is also a major drawback to all other fertility related therapeutic modalities and has been recognized to add significant handicap on infertile couples (14).

Finally, while the diagnostic accuracy of any given test is generally the most important criterion that is highly sought for before its utility in medical practice, this concept cannot be particularly met especially in the field of laboratory andrology. First, there is no gold standard test for fertility. In fact, no currently available test offers diagnostic information equivalent to those offered by SDF during the evaluation of infertile men (2,3,15). Second, the clinical usefulness of any given test may in certain circumstances out value its statistical significance, which is again the case with SDF testing. Therefore, it appears reasonable to recognize the clinical scenarios where SDF can be most helpful offering sound treatment modality that could improve the chances of conception among couples. The clinical guideline article by Agarwal *et al.* (1) is aimed towards achieving this purpose thereby encouraging SDF use in an appropriate clinical context providing solid grounds for future research and development for this important diagnostic modality.

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Footnote

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

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