Editorial

Call for wider application of sperm DNA fragmentation test

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Dr. Khandwala and Dr. Eisenberg in their insightful commentary discussed and endorsed the role of sperm DNA fragmentation (SDF) testing under specific circumstances in clinical practice (1). We concur with the authors that properly designed comparative studies, though ideal in providing the best quality evidence, are difficult to conduct in delineating the role of SDF testing in male infertility management. In fact, the American Urological Association Practice Guidelines Committee stated that the data on SDF testing was of low-quality level and mostly came from non-randomized studies (2). Although true, the higher level evidence on the clinical implication of SDF testing is being generated steadily. Lack of evidence to support treatment effect and absence of reporting live birth rate are among the most common criticisms of SDF studies. However, these concerns are also being addressed in several recent studies; a meta-analysis has concluded that men with lower SDF have significantly higher live birth rate after *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) (3). Another reported a significantly higher live birth rate with ICSI by using testicular sperm which has a much lower DNA fragmentation index (DFI) compared to ejaculated sperm in 147 couples (4). Another new study by Bradley *et al.* also reported on live birth rate after ICSI in 1,924 infertile couples. These authors reported that high SDF patients without an intervention [for example: physiological intracytoplasmic sperm injection (PICSI), intracytoplasmic morphologically selected sperm injection (IMSI), testicular sperm extraction (TESE), testicular sperm aspiration (TESA) or frequent ejaculation] had a lower fertilization rate and poorer clinical outcomes from blastocyst transfers as compared with low SDF patients; the fertilization rate was 66.0% *vs.* 70.2% (P=0.042), single embryo transfer (SET) fetal heart pregnancy rate was 28.5% *vs.* 45.2% (P=0.042), and SET live birth rate was 24.9% *vs.* 40.6% (P=0.060), respectively. The authors concluded that intervention (PICSI, IMSI, TESE, TESA, etc.) in high SDF patients with DFI >29% could achieve similar live birth rate as to low SDF patients (5). The results of these important studies were not available at the time when major clinical practice guidelines were set. The addition of valuable clinical data on SDF requires another review by the Professional Societies in reproductive field while we are looking forward to more well designed studies on SDF testing.

The authors raised concerns about the current quality of evidence particularly on the correlation of SDF with natural pregnancy and intrauterine insemination (IUI) outcomes. The number of reports on the relationship between SDF and natural pregnancy may seem scarce compared to reports on IVF/ICSI outcomes, but good quality data is not lacking. A meta-analysis involving 3 studies and 616 couples suggested high SDF determined by Sperm Chromatin Structure Assay (SCSA) was associated with failure to achieve natural pregnancy with an unambiguous odds ratio of 7.01 (95% CI: 3.68–13.36) (6). Time-to-pregnancy, which is an excellent endpoint in assessment of fertility potential in human study, was reported in two studies. In addition to the prospective LIFE study (7) as suggested by the authors, the Danish First Pregnancy Planner study provided solid evidence by illustrating the correlation between infertility and DFI

>30% in an unselected population of unknown fertility capability (8). Latest data provide further support for the use of SDF testing in fertility assessment and prediction of natural pregnancy. Sensitivity of 80–85% and specificity of 85–90% were reported with the use of sperm chromatin dispersion (SCD) and terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) assays (9,10). We concur with the authors that the correlation between high SDF and poor IUI outcomes is not without debate with several studies demonstrating strong correlation (11,12) while others failed to show such an association (13). Although the role of IUI in many fertility centers worldwide is declining which limits the acquisition of data. A recent study suggested SCSA DFI >27% has negative impact on IUI pregnancy rate supporting the correlation between high SDF and poor IUI outcome (14). Together with the knowledge that normozoospermic partners of infertile couples may have a higher level of SDF (15), poor sperm DNA integrity should be certainly listed as a sound possible etiology responsible for infertility in the patient of scenario #2 [unexplained infertility/recurrent pregnancy loss/IUI failure] of our practice recommendations (16). We consider the current evidence sufficient to support the use of SDF testing in that scenario.

The diagnostic accuracy of DNA testing deserves some discussion. The study by Evenson *et al.* was quoted by the authors and suggested that the specificity of the test reported is not satisfactory (17). We argue that the sensitivity and specificity of a diagnostic test depends on the cutoff values and its performance varies in accordance to the patient population. SDF test was used in both patients who were presumably fertile and patients who seek fertility counseling in the study by Evenson *et al.* However, in clinical practice, the test is applied only to high risk patients who are more likely to suffer from high SDF compared to general population. When SDF test is applied to the couples in scenario #2 of the practice recommendation (16) who had a history of recurrent miscarriages and IUI failure, the data from other patient group may not be applicable and the likelihood of false positive is probably much lower. In fact, recent data showed that SDF test by SCD, when used in a fertility clinic setting, had a sensitivity of 80.8% and specificity of 86.1% with a 26.1% cutoff of SDF index and a prevalence ratio of 2.84 for the occurrence of male infertility (9). A practice recommendation guiding the evidence-based application of SDF test in specific patient groups is therefore necessary to ensure satisfactory performance of the test.

It is reasonable that most of the Professional Societies [American Society for Reproductive Medicine (ASRM), American Urological Association (AUA) and European Association of Urology (EAU)] developing clinical practice guidelines are reluctant to make recommendations before more high quality clinical data becomes available in the literature. However, the application of a test should not be limited by clinical practice guideline alone; rather the decision to use a test in a clinical setting should be weighed not only by good science but more importantly by the magnitude of benefit it brings to a couple. In support of this argument are several advantages offered by the SDF test when done in the clinical setting: (I) identification of the possible underlying etiology in couples who are otherwise classified as unexplained or idiopathic infertility; (II) monitoring of treatment outcomes of either empirical or new treatment modalities; (III) stratification of patients to receive more targeted treatment for SDF; and (IV) avoidance of unnecessary workup and wastage of precious time and money in unproductive treatments.

The decision about the applicability of a clinical test is a fine balance amongst numerous factors with cost implication being a major consideration for the infertile couple and healthcare system. The authors pointed an important message that there is currently no literature on cost analysis of SDF testing as different fertility centers worldwide vary in their practice of assisted reproductive technologies (ART), not to mention the large difference in cost for the same treatment in different locality and different financing models. The issue becomes more complicated when it comes to infertility care as here the couples invariably desire a quick and effective treatment under a financial constraint (18). The presence of multiple intertwined and confounding factors in both male and female partners means that clinical decision should be individualized for each couple but there is no straightforward management algorithm. All these factors point to the fact that evidence-based cost analysis in using SDF testing may not be a realistic goal, or, at most, only apply to a specific subset of patients in a particular center. Esteves *et al.*, in their study, reported the number-need-to-treat in using testicular sperm to improve ICSI outcome (4). Such an approach we feel may serve as a basis for cost analysis studies. Currently, fertility treatments around the world are usually self-funded; however, with the decline in birth rate in some developed countries, comprehensive evaluation of cost effectiveness will become important as infertility treatment moves into population policy and public funding.

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Footnote

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

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