Editorial

Is National Institute of Clinical Excellence (NICE) guideline a nice guideline?

Ashok Agarwal[1], Chak-Lam Cho[2], Ahmad Majzoub[3], Sandro C. Esteves[4]

[1]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA; [2]Division of Urology, Department of Surgery, Kwong Wah Hospital, Hong Kong, China; [3]Department of Urology, Hamad Medical Corporation, Doha, Qatar; [4]ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil

Correspondence to: Ashok Agarwal. Professor and Director, American Center for Reproductive Medicine, Cleveland Clinic, Mail Code X-11, 10681 Carnegie Avenue, Cleveland, OH 44195, USA. Email: AGARWAA@ccf.org.

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We read with interest the well written commentary by Dr. Potdar (1) in response to the practice recommendations by Agarwal *et al.* (2). Dr. Potdar correctly pointed out the limitations of semen analysis in predicting outcome of assisted reproductive technologies (ART) and the role of sperm DNA fragmentation (SDF) tests in guiding treatment decision. The author highlighted a list of important clinical questions concerning the clinical application of SDF and agreed that the practice recommendations have successfully addressed all of them (1). Here, we would like to respond with further discussion on: (I) recommendation against varicocele repair for infertility from National Institute of Clinical Excellence (NICE) guideline; (II) treatment strategies for high SDF; (III) concerns about risk of aneuploidy from testicular sperm; and (IV) aim of the practice recommendations.

Clinical practice varies among clinicians and localities. It is also true that management should be individualized for each infertile couple according to the unique scenario. However, guidelines are proposed to summarize the best scientific evidence available at a time spot in answering an important and well defined clinical question. The primary aim is to set a basic standard care deliverable to patients and discourage potentially ineffective interventions (3). When the clinical question of 'does correction of varicocele improve pregnancy outcome?' is put up and analyzed by using the same body of evidence, it is hard to believe that completely opposing opinions come out from different professional societies. The value of varicocelectomy in the management of subfertile male is endorsed by American Urological Association (AUA) (4), American Society of Reproductive Medicine (ASRM) (5) and European Association of Urology (EAU) (6). In addition, AUA also suggested clear-cut criteria for varicocele repair in the Best Practice Statement (4). The suggestion from the various authorities is based on meta-analyses by Ficarra *et al.* (7) and Marmar *et al.* (8). Both meta-analyses reported improvement in natural pregnancy after varicocelectomy by only including patients with clinical varicocele and abnormal semen parameters. The meta-analyses specifically addressed the pitfall of the systematic review by Evers *et al.* (9) by inclusion of subclinical varicocele and normal semen parameters leading to heterogeneity of studies included. In a subgroup analyses of five randomized controlled trials in the latest Cochrane Review comparing treatment to observation in men with clinical varicocele and abnormal semen parameter, repair of varicocele result in favourable outcome with a combined odds ratio of 2.39 (95% confidence interval, 1.56 to 3.66) (10). Unfortunately, NICE guideline based its recommendation largely on the systematic review by Evers *et al.* (9) published in 2001 without considering more recent and larger body of evidence supporting varicocelectomy as treatment for male subfertility. The systematic review by Evers *et al.* (9) was regarded as level 1a evidence without recognizing its methodological flaw. Meta-analysis and systematic review is merely an analytic tool to summarize the vast quantity of clinical data. Selection of good-quality data is of paramount importance to ensure

generation of a reliable result. The inclusion of unfiltered heterogenous data will mask a significant outcome of a potentially beneficial treatment. It is the responsibility of fertility specialists in United Kingdom and worldwide to urge for a timely update on guidelines. The delivery of the best treatment to our patients should not be prohibited by an outdated guideline.

In addition to the use of antioxidants and testicular sperm in the treatment of high SDF, varicocele repair and sperm selection techniques represent the other major treatment strategies. A meta-analysis of six studies demonstrated a mean reduction of 3.37% in SDF after varicocelectomy (11). Sperm preparation technique including density gradient centrifugation has been attempted to isolate sperm populations with less SDF (12). However, there is concern that sperm from infertile patients with high SDF are more susceptible to further damage after processing (13). Hyaluronic acid binding method, sperm magnetic sorting and high magnification microscopy are among other proposed sperm selection techniques (14-16). Although the current techniques are still limited by the fact that none of them completely deselect sperm with DNA damage (17), the treatment effect of sperm selection based on motility and morphology with physiological intracytoplasmic injection and intracytoplasmic morphologically selected sperm injection has been revealed by a recent study (18).

The concern about risk of aneuploidy from testicular sperm is a valid one. In the study cited by Dr. Potdar, the incidence of mosaicism in embryo derived from testicular sperm extraction in men with non-obstructive azoospermia or oligozoospermia was significantly higher compared to embryos from intracytoplasmic sperm injection (ICSI) with ejaculated sperm (19). Another study that specifically addressed the aneuploidy rates in patients with high SDF may provide more relevant information to the concern: the aneuploidy rates between ejaculated and testicular spermatozoa in the same individual with persistently high SDF were reported. Although the aneuploidy rates is doubled in testicular sperm compared to ejaculated sperm (12.41% *vs.* 5.77%), SDF is reduced threefold (14.9% *vs.* 40.6%) (20). It is argued that the uncorrected high SDF would render natural pregnancy and intrauterine insemination unsuccessful. High SDF also negatively impacts pregnancy outcome after *in vitro* fertilization and ICSI with higher rates of pregnancy loss (21). The risk of genetic and birth defects of offsprings in ICSI candidates with high SDF cannot be eliminated without reducing level of SDF (21). A relatively small risk of aneuploidy by using testicular sperm in this group of patients may be justified by the substantial benefit offered by significant decrease in SDF, i.e., higher live birth rate (22).

Lastly, the practice recommendations proposed by Agarwal *et al.* (2) aim at transferring SDF test from laboratory bench to clinical practice. Cumulative experience and evidence from the last three decades on SDF tests were critically analyzed. The scenarios in the practice recommendations are considered appropriate to start the application of SDF testing clinically based on current best evidence. The practice recommendations serve as a kick-off and we contemplate wider clinical utilization of SDF testing with rapidly emerging data. We believe that the practice recommendations give food for thought not only for translational research, but also to clinicians alike. The panel brought together both researchers and clinicians and bridged the gap between laboratory and clinic. Nonetheless, research data must be translated to clinical practice before they will benefit patients. It is the high time to call for collaboration and effort among clinicians and researchers to further explore the potential of SDF testing.

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Footnote

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

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