Sperm DNA fragmentation testing

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Editorial

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We are proud to contribute an invited editorial on male infertility for the Journal of Evidence-based Women's Health Society. With this paper we are starting a new chapter at the EBWHJ, which from now on has a board of experts on male infertility and a section dedicated to this thematic area.

Male infertility is a disease of the reproductive system caused primarily by male factors includingdeficiencies in the semen, genetic and congenital conditions, anatomical, endocrine, functional or immunological abnormalities of the reproductive system, chronic illness and sexual conditions incompatible with coitus[1]. Worldwide approximately 8-12% of individuals trying to conceive are unable to do so, with the highest prevalence in Eastern Europe, North Africa, Middle East, Oceania and Sub-Saharan Africa[2].

Male factors, alone or combined with female factors, contribute to at least 50% of reported infertility cases. The psychosocial consequences of male infertility are severe, including the tendency to blame the other partner for the inability to conceive leading to stigmatization, isolation, neglect, depression and polygamy[3]. The prevention and management of maleinfertility is an integral component of comprehensive sexual and reproductive health services needed to attain a sustainable development goal.

Semen quality has been used as a surrogate measure of male fecundity for approximately 100 years. However, conventional assessment of semen characteristics including ejaculate volume, sperm count, sperm motility and sperm morphology rarely provides robust discriminatory information of the male fertility potential, unless at extremely low levels[4,5]. In recent years though, it became clear that semen of men facing difficulties to conceive may have abnormal levels of sperm with damaged DNA[6-9]. Apoptosis triggered by testicular conditions and oxidative stress (OS) during sperm transit through the male reproductive tract seem to be the primary causes of sperm DNA damage[10]. The source of OS can range from a specific clinical condition such as a varicocele or a subclinical genital infection to age, obesity, smoking, prolonged epididymal stasis and environmental or occupational exposure to toxicants[11-13].

Sperm DNA damage is associated with male infertility and decreased chances of conception, both natural and assisted[7,14]. Among pregnancies achieved by in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), the risk of miscarriage is increased if the male partner has elevated levels of sperm DNA damage in semen, thus leading to a decrease in the likelihood of live birth delivery[15,16]. Also, there is a concern that an underlying DNA damage could be transferred to the embryo by defective sperm and thus affect the health of resulting offspring[17]. Given the critical role of sperm DNA integrity for normal embryo development and pregnancy outcomes, assessments of sperm DNA damage have been used to obtain information about sperm DNA quality, particularly for the evaluation of a possible male factor contributing to infertility[8,18]. Most often, probes or dyes are used to identify the existence of DNA breaks in specimens examined by fluorescence and optical microscopy or flow cytometry[8,11,19]. The term 'Sperm DNA Fragmentation (SDF) has been used to broadly group these tests. The sperm chromatin structure assay (SCSA), terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), sperm chromatin dispersion test (SCD) and single gel electrophoresis (Comet) are the most

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commonly used methods to measure SDF currently[18].

Notwithstanding the remarkable evidence on the role of sperm DNA damage in infertility, a poor understanding of SDF assays' characteristics and a general belief that SDF is an untreatable condition has hampered the implementation of SDF testing in clinical practice[20-21]. The lack of guidance on which clinical scenarios SDF might be applied is also a criticism often heard[22]. To shed light on these critical issues, a clinical practice guideline (CPG), the first of its kind, was recently issued concerning the clinical utility of SDF testing in specific clinical scenarios[23]. The primarygoal of the guidelines was to underline the actual indications of SDF testing and to help doctors explain the management options available to patients with increased SDF (Box 1). The guidelines on the clinical utility of SDF testing based on clinical scenarios were arranged in two sections. In the first part, it outlines the current tests for SDF evaluation, pointing out their core principles as well as the main advantages and shortcomings whereas in the second part it includes an evidence-based analysis of test utility in clinical scenarios commonly found by practitioners providing care to infertility patients[23].

Specifically, the CPG on SDF testing based on clinical scenarios included varicocele, unexplained infertility, recurrent (natural) pregnancy loss, recurrent intrauterine insemination (IUI) failure, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) failures, and lifestyle risk factors[23]. In each clinical scenario, after a detailed discussion of the rationale involved, a clinical recommendation was made by the expert panel (Figure 1).

Recognizing the significant efforts from researchers that have moved SDF testing from bench to clinical practice in the 21stcentury, the Society for Translational Medicine has endorsed the CPG for SDF testing in male infertility[24]. With the publication of the above-mentioned CPG, a group of 58infertility experts from six continents and 22 countries contributed commentaries concerning their utility. The resulting work was compiled in an outstandingopen access supplement of Translational Andrology and Urology (seehttp://tau.amegroups.com/issue/view/612 or https://www.ncbi.nlm.nih.gov/pmc/issues/299972/). We recommend this supplement to clinicians and health care professionals involved in the management of infertile couples, including reproductive endocrinologists, urologists, gynecologists, andrologists, embryologists and nurses. Also, students and researchers in the biological and medical sciences interested in following the exponential growth in knowledge involving sperm DNA damage and infertility could benefit from this collection of articles.

We as the newly appointed board members in the area of male infertility are grateful to the executive editors of EBMWHJ for their initiative to include a thematic area dedicated to male infertility in theirfast-growing Journal. We hope our readersshare our excitement in the study of male infertility and sperm DNA damage and that they will appreciate this inaugural editorial of EBWHJ.

Fig. 1: Key issues of the clinical practice guidelines on sperm DNA fragmentation testing

1- The CPG on the clinical utility of SDF testing is timely to guide infertility specialists in requesting SDF tests in proper clinical scenarios
2- The scenarios coverspectrum of difficult clinical decisions that most fertility specialists encounter in clinical practice. The evidence-based recommendations are extremely valuable for assessment of male subfertility and couples undergoing ART
3- There is a common belief that SDF is untreatable. The guideline clarifies this issue and provides evidence-based guidance for interventions
4- SDF tests assess the quality of DNA packageand thus provide results distinct and more significant than those of conventional semen parameters
5- Sperm DNA fragmentation is a parameter with low biological variation and can be used as a surrogate marker of oxidative stress

CPG: Clinical practice guideline; SDF: Sperm DNA fragmentation; ART: Assisted reproductive technology

*Modified from Agarwal *et al.* The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility. Translational Andrology and Urology. 2017;6(Suppl 4):S720-S733. doi:10.21037/tau.2017.08.06

CONFLICT OF INTEREST

There are no conflicts of interest.

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