Commentary

Evidence based sperm DNA fragmentation

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Male factor infertility is an important and current issue in the field of human reproduction. The prevalence of male factor associated infertility is increasing with almost 50% of all cases of fertility treatments being linked to this factor (1). Moreover, the introduction of intracytoplasmic sperm injection (ICSI) in 1992 (2) offered, for patients with severe male factor infertility, the opportunity of conception and allowed the scientific community to better understand not only the aspects of male factor but also the accurate indications for ICSI (3).

The post-ICSI era opened a new dilemma and paradigm: nowadays, it is absolutely essential to understand and improve male factor investigation aiming to increase the pregnancy rates in this group of patients.

One of the most important principles of evidence based medicine (EBM) is to give the best evidence after a critical review, considering the advantages and flaws of a specific topic.

The field of human reproduction is unique in a way where it is especially hard to give the best evidence pertaining to a certain treatment. The primary outcome after an in vitro fertilization (IVF)/ICSI treatment is delivery of a healthy baby, but success rates are relatively low (25–30%) and affected by several variables, including age, type of fertility, controlled ovarian stimulation, obesity, smoking, and life-style factors. Therefore, several times we only describe the most appropriate evidence (not the best) regarding patients suffering from infertility (4).

Conventional semen analysis is fundamental for all couples seeking fertility treatment, but it is only a screening method (5). The parameters and interpretation (cut-off/threshold) are absolutely arbitrary, lacking good epidemiologic and clinically acceptable evidence. In recent years, several papers have aimed to describe the clinical utility and significance of sperm DNA integrity in IVF cycles. The body of evidence is fair regarding the decrease in implantation rates, embryo score and even pregnancy rates in patients with a higher DNA fragmentation (6).

However, analysing the existing evidence, Agarwal *et al.* (7) recently described numerous problems and unsolved questions not only associated to sperm DNA integrity, but also to the methods and indication for DNA fragmentation testing in male factor infertility.

There are several methods to examine DNA fragmentation in the semen: AO test, AB staining, CMA3 staining, TB staining, TUNEL, SCSA, SCD and SCGE. But, the majority of tests are semi-automatized, observer-dependent, requires an experienced and a skilled person.

Another significant question is the absence of a clear gold-standard method. TUNEL is considered a gold standard, but is far to be the ideal method as it lacks standardization and fails to correlate with a clear clinical outcome.

Another consideration is about the utility and variability of SDF testing. The authors outlined that there are several clinical situations in which DNA fragmentation is increased and could be associated with an unfavourable reproductive outcome. However, we do not have a randomized clinical trial with a large number of patients to determine a definitive conclusion.

Using sensitivity analysis, Osman *et al.* (6) in a recent systematic review concluded that after ICSI, higher sperm DNA fragmentation did not change birth rates. The authors recommended that more clinical trials should be done before a definitive conclusion is reached.

Agarwal *et al.* discussed the pathophysiology of sperm

DNA fragmentation stating that several mechanisms were described including higher testicular temperature, oxidative stress, cell destruction, lipid metabolism and lifestyle exposures. Moreover, the authors also debated the etiology of SDF, linking to conditions such as varicocele, life-style factors, genito-urinary infections, radiation/chemotherapy and gonadotoxin exposure.

In addition, the authors outlined the indications of sperm DNA fragmentation testing: varicocele, unexplained infertility, recurrent pregnancy and IUI/IVF loss and presence of lifestyle factors. However, the strength of evidence linking DNA fragmentation to these outcomes are weak. We really need more controlled and properly designed studies, including a large number of patients to reach a good epidemiological conclusion.

Furthermore, there are several alternatives to treat patients with a higher sperm DNA fragmentation: oral anti-oxidants, varicocele ligation, frequent ejaculation, Intracytoplasmic injection of morphologically selected spermatozoa and even a testicular sperm extraction. Nonetheless, good clinical evidence is also lacking to support these alternatives.

The paper by Agarwal *et al.* is unquestionably up-to-date and outlines the most relevant aspects of this new alternative in terms of male factor investigation.

We really need more studies from bench to bedside to better understand the physiology and clinical usefulness of sperm DNA fragmentation, considering the relevance and prevalence of male factor in human reproduction.

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Footnote

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