Commentary

Is the sperm DNA status the best predictor of both natural and assisted conception?

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The number of articles on the clinical significance of sperm DNA integrity and/or fragmentation has been increasing during the last 2 decades. Despite substantial evidence, official recommendation to introduce sperm genomic integrity tests into the routine evaluation of 'male factor' is lacking. The review by Agarwal and co-authors (1) summarized promising results for clinical utility of sperm DNA fragmentation tests. Based on their own large experience, the authors demonstrated four different cases of infertile men, in which the evaluation of sperm DNA quality can be recommended. Although the study provides useful prognostic information for practitioners who treat infertility, some critical questions remains unresolved.

As for sperm DNA fragmentation measurement, variability among the individuals, medical interventions and methodology have been the main cause of conflicting results. In this context, we have "high hopes" associated with the development of new quantitative epidemiological statistical tools providing the opportunity to combine data from the multiple independent studies and to consolidate the conflicting results. In fact, several previous meta-analyses, also from the author's group, demonstrated some positive clues that sperm with DNA damage may provoke detrimental outcomes of the *in vitro* fertilization procedures including decreased pregnancy rates and/or increased miscarriages (2-4). However, in contrast to the study by Agarwal and co-authors, other researchers found no association between sperm DNA fragmentation and clinical outcome of medically assisted reproduction using a systematic review and meta-analysis (5). At this point, it should be emphasized that the value of a meta-analysis provides a useful ground for formal recommendations but it does not provide the definitive answer to the question for the future of the assessment of sperm genomic integrity. Randomized controlled trials in the field are still very limited. There is a need to conduct more prospective studies, including large numbers of patients, a wide range of analyzed semen parameters, patient characteristics and a reproductive outcome.

The etiology of sperm DNA damage is complex and multifactorial. On the basis of clinical and experimental results, three different molecular and biochemical pathways have been proposed to explain the etiology of sperm DNA fragmentation: complexity of sperm maturation process, incomplete apoptosis in testis and free radical attack (6). There is now increasing evidence that the majority of sperm DNA breaks are of oxidative origin. In this context, the recommendation of Agarwal and co-authors for determining of the level of sperm DNA fragmentation in infertile men with evidence of exposure to environmental and lifestyle factors linked with oxidative stress is well justified (1). However, it is important to remember that the three above-mentioned pathogenic mechanisms may contribute in various proportions to the DNA status in sperm arriving to the ejaculate. It is estimated that DNA damage observed in ejaculated spermatozoa may be partially caused by post-testicular defects during sperm transit (7,8). Regardless of these interesting findings, the origin of DNA damage in the male germ line still presents a puzzle. Despite a range of DNA evaluation techniques, none of currently available assays provides reliable information on the nature of sperm DNA breaks and their origin. Without accurate knowledge

of the mechanisms responsible for the induction of DNA breaks in ejaculated spermatozoa, sperm DNA tests are still poor predictors of negative or positive pregnancy outcomes.

Among the various techniques used to study DNA fragmentation in sperm cells, a direct terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL) assay has been most frequently used and found to be closely correlated with male infertility, compared to other indirect tests such as the sperm chromatin structure assay (SCSA), the sperm chromatin dispersion test (SCD) and comet assay at alkaline pH (9). However, TUNEL methodology can be significantly influenced by highly compacted nature of sperm chromatin as well as sperm viability (10). Interestingly, the relationship between sperm DNA integrity and routine sperm vitality parameter has been demonstrated with respect to SCSA (11). This was the first study which proposed sperm vitality as a predictor for the level of sperm DNA fragmentation. In light of this finding, there is no need to perform the expensive sperm DNA fragmentation tests during infertility work-up in men with high (≥75%) as well as with low (≤30%) levels of sperm vitality. And thus it justifies the elimination the need for sperm DNA integrity measurements in the majority of men which remains in contrast to the opinion extended by Agarwal and co-authors (1).

The increase in the percentage of sperm with fragmented DNA has often been reported in ejaculates from subfertile and infertile men with clinical conditions associated with oxidative stress and apoptosis, including varicocele, idiopathic infertility, and urogenital tract inflammations/infections. During bacterial genitourinary infections, inflicted changes to sperm DNA can be attributed to both leukocytes and bacteria; and the results of clinical studies indicated that the evaluation of sperm membrane or mitochondria potential rather than DNA status can be an important information to predict the chance of fertilization and can be a significant step towards establishing new diagnostic algorithms for studying bacterial influence on sperm quality (12). One of the subgroups which may benefit from sperm DNA integrity evaluation is the group of patients with varicocele. There are some promising data regarding diagnostic accuracy of sperm DNA degradation index measured by SCD test as a potential noninvasive biomarker to identify men with varicocele-associated infertility (13). The role of the assessment of sperm DNA fragmentation in the context of selection of patients for varicocelectomy was also discussed by Agarwal and co-authors (1). Although the available data derived from uncontrolled studies indicate that surgical treatment of varicocele is associated with improvements in sperm nuclear DNA integrity, randomized prospective clinical trials are needed to provide a clinical indication for routine use of the sperm DNA integrity assessment in infertility evaluation of men with varicocele.

In view of the increasing number of cases of infertility caused by "male factor", current research efforts are focused on the search for new non-invasive and sensitive seminal diagnostic biomarkers offering new perspective in clinical practice. Even after almost 40 years of intensive work, sperm DNA integrity has not become an independent determinant of male infertility. However, the changes in DNA strand breakage, which often occurs in the male germ cells due to the lack of their own DNA repair system, are critical for the quality of embryos and for the achievement of an ongoing pregnancy. We should also remember that the predictive value of sperm DNA fragmentation depends not only on a number of factors from the male side but also on female ones (e.g., oocyte quality) which greatly contribute to the successful establishment of natural and/or assisted procreation (14,15). In our view, the comprehensive recognition of different sperm defects may open new diagnostic and therapeutic possibilities in impaired male fertility. Recently, the importance of sperm mitochondria and membrane depolarization for sperm fertilizing potential have been highlighted (12,16). Novel tests evaluating the structure and functions of sperm cell organelles (including DNA) are now being developed worldwide.

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Footnote

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

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