



The Possibility of Increasing Oocyte Capacity to Repair Sperm DNA Fragmentation

During spermatogenesis, the sperm loses most of its cytoplasm and acquires a shape commensurate with its main function for transferring the paternal genome to offspring through fertilization of oocyte and formation of early embryo. The different shape of mammalian sperm compared to somatic cells enables the sperm to pass through difficult pathways to reach and fertilize oocyte. Although the facilitating role of sperm's structure and morphology in reaching the oocyte is significant, sperm chromatin condensation is consequential for protection of the paternal genome from harmful external and internal factors. Despite specific structure of sperm chromatin and changes in its nuclear proteins for greater compaction and protection against harmful agents, sperm is vulnerable to harmful agents such as free radicals since it loses most of its cytoplasm. However, seminal fluid plays a major role for protection of sperm when it has close contact with the seminal fluid.

Normal semen contains sperm (Motile, immobile, and dead) and non-sperm cells, including epithelial cells, immature germ cells at different stages, leukocytes (WBC), and cell debris suspended in a mixture fluid from the testes, epididymis, and accessory sex glands. Increased defective sperm, dead cells, leukocytes, bacteria, and cell debris or removal of seminal fluid during sperm processing can disrupt protective effects of semen culminating in damages to sperm chromatin and its membrane. In addition, other factors such as infections, smoking, drug addiction, exposure to environmental and occupational pollutants, aging, varicocele, high fever, increased testis temperature (Using laptop, hot baths, and tight clothes), paralysis by spinal cord injuries, chronic diseases such as diabetes and kidney failure are associated with increased sperm DNA fragmentation (1).

Therefore, the assessment of sperm chromatin damage and DNA fragmentation index (DFI) has received special attention by researchers and clinicians for diagnosis and treatment of male infertility, so it is often requested as a complementary test with semen analysis in IVF clinics. The DFI more than 30% is associated with reduced natural male fertility, risk of miscarriage, longer time to conceive, fertilization failure, low quality embryos, implantation failure, and repeated IVF cycles (2).

However, the importance and role of DFI in assessment of male infertility and its measurement methods were widely criticized by the time of its introduction. However, extensive research gradually established its role in diagnosis and treatment of male infertility and also its measurement methods were somewhat improved and standardized. Therefore, based on the DFI results, a variety of new pharmacological and surgical therapeutic strategies have been recommended and evaluated for improvement of male fertility (1).

A number of clinical and surgical interventions including changes in lifestyle, ejaculatory abstinence, oral antioxidant therapy, hormone therapy, varicocele repair and testicular sperm extraction (TESE) are suggested to improve sperm quality and reduce DFI. Oral antioxidant supplementation in infertile men with oxidative DNA damage could reduce the sperm DFI and significantly enhance sperm chromatin integrity. Recent studies have shown that shorter intervals between ejaculations improve DFI and sperm quality, which is associated with better intrauterine insemination (IUI) and assisted reproductive technology (ART) outcomes compared to recommended time for semen analysis. The sperm retrieved through testicular sperm extraction (TESE) in men with high levels of DFI has better DNA quality and lower DFI than ejaculated sperm following repeated IVF failure. The use of testicular sperm leads to an increase in fertilization rate, good quality embryos, implantation rate, and pregnancy rate compared to ejaculation in ICSI cycles among men with high level of DFI and resistance to drug interventions (3).

In addition to mentioned interventions, an issue that has raised more attention is the role of the oocyte in repairing sperm DNA fragmentation. Oocytes are able to repair fragmented DNA following fertilization. The repairing system depends on the cytoplasmic and genomic mechanism and the quality of oocytes. The qualified early embryos also have the ability to repair remaining DNA breakage during pre-implantation at cleavage stage. However, the repairing ability of the oocyte has a limited capacity and vast amount of damage in two strands of DNA can not be properly repaired which may lead to fertilization failure, poor quality of embryo, and finally IVF failure (4, 5).

The goal of above clinical and surgical interventions was to reduce the incidence of sperm DNA fragmentation. However, the main question is how to increase the oocyte to maximize its repairing capacity. In

other words, the chief concern is whether our current practices in IVF cycles including type of ovarian stimulation protocol, denudation, micro-manipulation, length and quality of *in vitro* culture before and after fertilization are effective in changing the potential of oocyte in repairing sperm DNA fragmentation. In fact, further research needs to be conducted to evaluate whether special adjuvant therapies in induction of ovulation cycles would increase the repairing potential of oocytes. It seems that the possibility of adding specific ingredients or components to embryo and oocyte culture media to increase the repairing potential of oocyte can be a tentative hypothesis.

Answer to these questions necessitates considering some ethical aspects that limit the possibility of study and research on the human oocyte and embryo; therefore, designing a series of animal studies for future research in the field of male fertility, with a focus on andrology, is an appropriate strategy which may be conducive to success of infertility treatment cycles. In fact, changes in lifestyle, increased occupational and environmental pollutants, and other harmful factors have led to threats to male fertility and subsequently sperm DNA fragmentation. It seems that along with all protocols for reduction of sperm DNA damages in various aspects of life and occupational and environmental practice, different solutions must be devised for *in vitro* and *in vivo* repairing of sperm DNA damages in future.

References

1. Evgeni E, Charalabopoulos K, Asimakopoulos B. Human sperm DNA fragmentation and its correlation with conventional semen parameters. *J Reprod Infertil.* 2014;15(1):2-14.
2. Kim GY. What should be done for men with sperm DNA fragmentation? *Clin Exp Reprod Med.* 2018;45(3):101-9.
3. Esteves SC, Santi D, Simoni M. An update on clinical and surgical interventions to reduce sperm DNA fragmentation in infertile men. *Andrology.* 2020;8(1):53-81.
4. Ménézo Y, Dale B, Cohen M. DNA damage and repair in human oocytes and embryos: a review *Zygote.* 2010;18(4):357-65.
5. Ješeta M, Myšková M, Žáková J, Crha I, Crha K, Chmelikova E, et al. Can oocytes repair fragmented DNA of spermatozoa? *Med J Cell Biol.* 2020;8(2):73-7.

Mohammad Reza Sadeghi
Editor-in-chief