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Editorial

The Necessity to Retrieve Testicular Sperm in Infertile Non-Azoospermic Men with High Levels of SDF

Sperm cell's shape and structure is different from other cells. The overall structure of the sperm has changed to suit its morphology to the main functions for transmission of biological information and paternal genome to the next generation. Therefore, most of the alterations during spermatogenesis and spermiogenesis include the loss of most of its organelles, cytoplasm, and chromatin compaction impair its defense mechanism and predispose sperm to damages by environmental factors. One of the most protected and critical part of sperm is its chromatin located in the head of spermatozoa. Sperm chromatin, despite being ten times more compact than other cells, is easily damaged by endogenous and external factors, leading to fragmentation of sperm DNA. For nearly one decade, sperm DNA fragmentation has been considered as one of the causes of male infertility and various methods have been proposed and used for evaluation and measurement of sperm DNA fragmentation (SDF) (1).

In many infertile men, it is observed that despite performing various required interventions and medical treatments, the level of SDF remains high. There is adequate evidence that sperm DNA fragmentation is associated with poor ART results; therefore, SDF may exert negative effect on assisted reproduction and pregnancy outcome. Sperm chromatin integrity is essential for normal development of early embryo, successful pregnancy, and healthy live birth (2).

The number of published articles in this field is continually growing. As of today, more than 2,000 articles on sperm DNA damage have been indexed by PubMed, half of which are published in the last 5 years. Also, a large number of them are concerned with the tests for selection of vital sperm with the lowest level of SDF for ART and many are focused on comparison of different SDF quantification methods.

Analysis methods for SDF application determine the different features of DNA breakdown, while these characteristics relate to the properties of the DNA molecule. The ideal method for measuring SDF has not yet been introduced, so the limitations and potential benefits in clinical outcomes should be thoroughly investigated for selection of the effective analysis method in SDF application. It seems that such procedures to measure SDF level are not completely accurate and reliable until proposing a golden standard method for this purpose. Therefore, depending on the exigency of the circumstance, a reliable SDF measurement method with an appropriate threshold should be used (1, 3).

One of the proposed interventions in infertile men with high levels of DNA fragmentation index (DFI) is to use retrieved testicular spermatozoa instead of ejaculated ones with reasonably lower SDF. The use of testicular sperm may be a suitable alternative to obtain a sample with less DNA fragmentation in couples who experienced recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL) due to high levels of SDF. However, the SDF assays have been optimized to only measure the fragmentation of sperm DNA in ejaculate and their efficiency has not been approved for assessment of testicular sperm, making it difficult to interpret testicular SDF levels (1, 2).

On the other hand, it has been well recognized that most of sperm DNA fragmentation is triggered by post-testicular sperm exposure to oxidative stress in the epididymis and vas deferens. Sperm DNA damages progressively increase from the seminiferous tubules to the epididymis and vas deferens with the highest level in ejaculation (4).

Infertile men with increased level of SDF in semen can benefit from retrieved testicular spermatozoa for intracytoplasmic sperm injection (ICSI). However, testicular sperm appears to be desirable in ICSI when SDF level is low, yet elevated aneuploidy rates in testicular spermatozoa counteract such potential benefits. Testicular aneuploid sperm can fertilize an egg and lead to a successful pregnancy. In spite of its low risk, the rate of having a child with an aneuploidy is higher in such cases in comparison to other types of infertility (5).

Literature review has shown that SDF has no significant impact on fertilization, cleavage and early pregnancy rate, but the rate of pregnancy loss is significantly higher in comparison to cases with lower SDF. The main problem in interpreting and applying the results of such studies is their retrospective nature and heterogeneous designs with different methods for evaluation of SDF. Recent international clinical guidelines recommend the use of testicular sperm in cases with a history of at least two recurrent pregnancy losses following ART and using ejaculated spermatozoa; however, before performing TESE-ICSI for these couples, it is necessary to

receive thorough consultation and try all strategies to reduce SDF before performing this invasive and traumatic procedure. Clinical management of infertile men with high level of SDF should be considered as the first-line infertility treatment before performing invasive procedure of testis biopsy. Controlling the effect of all harmful factors on sperm chromatin, including treatment of underlying diseases such as obesity, diabetes, infection, smoking control, frequent ejaculation before ART, and the use of appropriate antioxidants can improve sperm chromatin integrity. Along with all these strategies, the selection of the sperm with intact chromatin using physiological ICSI (PICSI), IMSI, and MACS methods can reduce the effects of sperm chromatin damage on ART results (2, 3).

Although many researches advocate the use of testicular sperm retrieval in normozoospermic men with RIF and RPL due to increased levels of SDF, most of their studies are categorized as small cohorts, case series, or case-control studies with unreliable evidence, inappropriate design, lack of proper control group, limited comprehensiveness, ignoring the role of female factor, ungeneralizable results, lacking statistical power which are solely confined to chemical and clinical pregnancy disregarding miscarriages and live birth rates. Therefore, prior to wide application of testis biopsy in these cases, a series of new and well-designed studies with detailed plan, inclusion of control groups, and appropriate outcome measures are essential to compensate for the drawbacks of previous studies and scientifically prove the priority of testicular sperm to ejaculate in cases with high SDF who are unresponsive to other first-line interventions.

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