Sperm DNA fragmentation: What have we learned so far?

The standard evaluation of an infertile couple hinges on assessments of ovarian reserve, the female genital tract, and semen parameters. However, this evaluation omits the impact of the male gamete. Indeed, a couple's infertility is attributable to the male partner in as many as 50% of cases. Thus, identifying subtle male factor infertility is valuable, particularly when treating couples in which the male partner has a normal semen analysis, and the female partner has a negative infertility workup. Although not recommended by the joint American Urological Association and American Society for Reproductive Medicine guidelines as a part of the initial male infertility evaluation, sperm chromatin fragmentation (SCF) assessment has been recognized as a useful tool in cases of persistent assisted reproductive technology failure and recurrent miscarriages (1).

SCF occurs when there are single- and/or double-stranded DNA breaks in the linker region of the sperm DNA not bound to protamine and, therefore, more prone to damage. Although different tests are available, the sperm chromatin structure assay is considered the gold standard; the most sensitive test is the Single Cell Gel Electrophoresis assay, also known as Comet assay, with its two variants, alkaline or neutral, which are capable of distinguishing single- or double-stranded DNA breaks. The most used tests are the sperm chromatin dispersion and the terminal deoxynucleotidyl transferase–mediated fluorescein-dUTP nick-end labeling (TUNEL) assays. In our laboratory, we find the TUNEL assay to be less subjective and capable of screening few available spermatozoa, such as in cases of severe oligozoospermia or surgically retrieved specimens.

Although SCF appears to have a greater impact on embryo development and implantation in programmed intercourse, intrauterine insemination, and standard in vitro insemination (IVF) (2), its effect is less apparent in couples treated by intracytoplasmic sperm injection (ICSI). This may be explained, particularly in IVF, by the fact that the gametes are not exposed to reactive oxygen species and catabolites generated by decaying cells from the sperm sample during overnight incubation. Moreover, with ICSI, a morphologically normal and motile spermatozoon is selected arbitrarily (3). Nonetheless, if SCF is prominent, it will affect embryo implantation even with ICSI.

The current study by Voncina et al. (2) attempts to identify, in a patient population routinely screened for DNA fragmentation index (DFI), the impact of a compromised sperm genome on IVF and ICSI outcomes. Although it is well designed and includes a well-proven test, the study is limited by being a cohort study and lacks randomization. It fails to identify a specific causality or even a relationship between sperm DFI and clinical pregnancy, limiting its findings to an association between DFI and pregnancy loss. Thus, the poor correlation shown justifies the approach outlined by American Society for Reproductive Medicine guidelines that routine sperm DFI analysis should not be performed. The study also does not discriminate between the severity of the SCF nor the type of breakage (single- vs. double-stranded DNA). Nonetheless, the investigators should be commended for successfully recruiting a large, homogeneous study population. However, by only using ejaculated spermatozoa, they could not measure the impact of an alternative sperm source or a different sperm-processing method on the clinical outcome.

The most important question remains: What should be done in cases of severe sperm DNA fragmentation? It has been shown that as spermatozoa progress through the male genital tract, the chances of DNA damage increase (4). From this, the use of surgically retrieved spermatozoa may prove beneficial for couples in which the male partner has elevated and persistent high SCF. Moreover, the clear and inverse relationship between SCF and sperm motility supports an alternative to the surgical retrieval approach and proposes the use of spermatozoa selected through a microfluidics chamber (5). While all these efforts are aimed at identifying the spermatozoon with the highest motility and superior genomic integrity, we should not overlook advanced maternal age—with its inherent oocyte aneuploidy—as a major adverse factor in reproductive outcomes.

In the meantime, to continue our pursuit of identifying the ideal spermatozoon, all investigations aimed at clarifying the stealth cause(s) of infertility, such as the study in question, are welcome.

Philip Xie, B.S.
Stephanie Cheung, B.S.
Olena M. Kocur, B.A.
Zev Rosenwaks, M.D.
Gianpiero D. Palermo, M.D., Ph.D.
The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, New York

https://doi.org/10.1016/j.fertnstert.2021.09.029

REFERENCES

1. Schlegel PN, Sigman M, Collura B, De Jonge C, Eisenberg ML, Lamb DJ, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. Fertil Steril 2021;115:P54–61.
2. Voncina SM, Stenqvist A, Bungum M, Schyman T, Giwercman A. Sperm DNA fragmentation index and cumulative live birth rate in a cohort of 2,713 couples undergoing assisted reproduction treatment. Fertil Steril 2021;116:1483–90.
3. Palermo GD, Neri QV, Cozzubbo T, Rosenwaks Z. Perspectives on the assessment of human sperm chromatin integrity. Fertil Steril 2014;102:1508–17.
4. Xie P, K D, Parella A, Cheung S, Rosenwaks Z, Goldstein M, et al. Sperm Genomic Integrity by TUNEL varies throughout the male genital tract. J Urol 2020;203:802–8.
5. Parrella A, Keating D, Cheung S, Xie P, Stewart JD, Rosenwaks Z, et al. A treatment approach for couples with disrupted sperm DNA integrity and recurrent ART failure. J Assist Reprod Genet 2019;36:2057–66.