

# Using sperm testing to improve patient and offspring health: rational, evidence-based care of the infertile male in the ART clinic

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In the modern world of infertility care, two realities facing most clinicians are the basic fact that in many situations limited financial resources are available to address the couple's infertility, and second, couples desire to treat their infertility as quickly as possible (1). These factors have unfortunately justified in the minds of many clinicians the rush to the assisted reproduction therapy (ART) clinic and treatment with intracytoplasmic sperm injection (ICSI), rather than traversing the morass of sperm assays with limited standardization and validated performance characteristics and usage guidelines (2,3). While the discovery of ICSI is undoubtedly the most useful development in infertility care since the introduction of *in vitro* fertilization (IVF), it has also unfortunately contributed to the decrease in efforts to accurately diagnose underlying etiologies and medically and surgically address the etiologies (4, 5). In the review by Agarwal *et al.*, we have a measured, rational explanation of the differences in sperm DNA damage assays, as well as a concise review of the data regarding medical and surgical intervention in patients with sperm DNA fragmentation (6).

Agarwal *et al.* provide a rational proposal for integration of sperm DNA fragmentation testing in the clinic in this era of ICSI, despite inherent limitations in drawing evidence-based guidelines. Much of the confusion and delay in utilizing sperm assays in general, and also true for DNA fragmentation testing, has been due to uncertainty in the literature due to multiple assays with inadequate efforts to standardize the assays between laboratories (7,8). This has led to almost negligible success in developing quality

consensus of care standards. In their review, Agarwal and al. provide a thumbnail description of the assays available to analyze sperm DNA fragmentation, including both direct and indirect assays. While indirect assays, such as aniline blue staining, chromomycin A3 staining, and toluidine blue staining, are associated with DNA fragmentation, it must be remembered that they are, at best, indirect measures of DNA damage and crude measures of chromatin composition. While their inclusion as assays is helpful in framing the discussion needed for further validation studies, they should not seriously be included as possible clinical measures of DNA damage. Until studies can clearly distinguish difference in the predictive powers of the various assays, after standardization of techniques between labs, the literature will remain muddy and high level evidence-based guidelines can not be developed.

Rather than including indirect assays as a possible assay of DNA damage, it is likely that a more prudent pathway for development of an ideal evaluation of male infertility would include a direct measure of sperm DNA damage and a separate marker of sperm chromatin packaging (histone and protamine composition) competence. Further, it is important to remember that the various "direct" assays differ in their ability to detect actual *vs.* potential DNA damage, as well as single *vs.* double stranded DNA breaks (9,10). Each of the assays have been utilized in clinical studies with no firm conclusions yet reached on which assay is actually most helpful for clinical use. Until this issue is resolved, large scale studies to clarify the exact impact of DNA fragmentation on fertility outcomes will remain

impossible due to the bias introduced by multiple non-standardized assays. Lastly, ultimately an ideal measure of sperm fragmentation measure would render the sperm useable after the assay in cases where the couple was using the sperm for IVF/ICSI or IUI (11). While this is certainly a longer-term goal, we should not lose sight of this objective.

Perhaps the strength of the guidelines presented by Agarwal *et al.* is the scope of testing suggested (6). Clearly, data are not available at this time to suggest routine screening of all men evaluated at a fertility clinic, even with the poor predictive power of the routine semen analysis. The authors carefully review the data on sperm DNA fragmentation and varicoceles, improvements after varicocelectomy, unexplained infertility, and poor IVF outcome and recurrent pregnancy loss, and suggest usage in such cases. The use of the assay in these specific patients is evidence-based and should be implemented in ART clinics not currently employing such assays. It is possible that more focused utilization of DNA damage assays will also aid in identifying assays with the most predictive power for clinical use and improve standardization. Further, it may also allow refinement of subtypes of male infertility allowing more precise treatments for selected patient populations.

A major focus of current research in reproduction is the role of environmental factors on gamete and embryo competence, as well as long-term health of offspring (12,13). An improving understanding of gamete, embryo, and offspring epigenetic modelling and remodeling has opened the doors to better linking environmental disruptors to disease. While the mechanisms are not yet resolved, it is entirely possible that the major sequelae of sperm DNA damage are disruptions and/or alterations in the sperm, and ultimately embryo, epigenome (14-16). Secondly, it is important to remember that sperm DNA damage is likely, at least partially, the result of inadequate packaging of the DNA in the highly compacted sperm chromatin, or in other words, a disruption of protamination (16). These two caveats highlight the need for future mechanistic studies to evaluate not only DNA strand breaks, but also chromatin composition and epigenetic marks.

The list of environmental factors potentially affecting sperm DNA damage and the sperm epigenome is large and growing (17,18). Agarwal *et al.* succinctly and soundly review the data for various environmental factors and suggest sperm DNA damage testing in patients with relevant exposures. While one could argue that another approach is to empirically counsel such patients to alter their lifestyles

without sperm data, it seems obvious that efforts to promote a healthier lifestyle would be strengthened with laboratory data demonstrating a potentially correctable defect. While cessation of medications or lifestyles affecting DNA damage is both logical and evidence based, the authors briefly highlight the scant data for testicular sperm harvesting, sperm separation techniques, and anti-oxidant therapy, each of which may ultimately find clinical usage niches but are currently not validated.

Additionally, a plethora of data now exists linking reduced male fertility to poor somatic cell health (19,20). While the mechanisms of this remains unknown, DNA fragmentation as well as epigenetic and genetic aberrations are likely candidates to explain this relationship. Sperm DNA fragmentation testing may ultimately be useful in elucidating possible mechanisms. As accumulating data are now linking male infertility to not only individual health and longevity but also familial health and longevity, understanding this relationship may be crucial to improving population health.

Ultimately, the question that we as individuals and as a medical community must consider is if we are providing the best care to the infertile male, the couple, and the offspring by ignoring the “health” of the sperm. Further, we must honestly confront the financial incentives that may impact the decision of whether to fully workup the male or bypass male factor infertility through ICSI. Recent data clearly indicate that sperm DNA damage is associated with reproductive health issues in the male and in the embryo. In their manuscript, Agarwal *et al.* provide clear, evidence-based guidelines that should facilitate practical implementation of sperm DNA damage testing in the clinic with the objective of not only improving ART success rates, but more importantly to improve the health of the father and the offspring.

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## Footnote

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

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