Commentary

Practical considerations for DNA fragmentation testing in the management of male fertility

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Over the past decade, the importance of DNA fragmentation has matured as more studies suggested a role in the management of male fertility. As a measure of spermatogenic damage from reactive oxygen species (ROS), DNA fragmentation occurs primarily during post-testicular processing through the epididymis (1,2). Given that spermatozoa are exquisitely sensitive to oxidative stress, varicoceles, a known cause of elevated ROS levels, are theorized to be one of the major contributors.

In this issue of *Translational Andrology and Urology*, Agarwal *et al.* (3) present a well-written review highlighting several key issues dealing with the management of men with high levels of sperm DNA fragmentation. Agarwal *et al.* (3) correctly point out that DNA fragmentation rates are reduced post varicocele repair (4). As such, decreases of sperm DNA fragmentation following varicocele repair can improve outcomes when ejaculated sperm are used for natural conception; as well as in cases where assisted reproductive technologies (ART) are required (3).

While the article draws attention to the basic concepts, practical "real-world" experiences may be different. Consider for example, a patient who is already in the process of undergoing *in vitro* fertilization (IVF) and has high DNA fragmentation. On referral to the urologist, physical examination reveals grade 3 varicocele(s) and testicular atrophy. With a direct cause for the elevated DNA fragmentation identified, consideration needs to be given as to the best management approach.

Agarwal *et al.* (3) detail one option: repair of the varicocele and future conception using ejaculated sperm (either natural conception or with ART). This would require several steps including delaying/cancelling the current IVF cycle. Moreover, further testing would be required with no guarantee that DNA fragmentation rates could be improved. Significant costs and delay to the patient would invariably result.

The options that remain include testicular extraction (TESE) with, or without, concurrent varicocele repair. This approach would not result in cancellation of the current IVF cycle. The difficulty lies with the required timing of the surgical interventions. Since evidence exists that cryopreservation increases DNA fragmentation (5,6), it would stand to reason that a fresh sample would yield the best results. Timing a fresh sample and a concurrent varicocele repair becomes exceedingly difficult- but not impossible.

Future studies examining outcomes from fresh testicular sperm harvests in the presence of varicocele(s) could prove interesting and shine some light on how to best proceed in the aforementioned situation. Furthermore, the best method of sperm harvest should also be further delineated in these cases. In my practice, testicular sperm aspiration (TESA) under a local anesthetic using a 19-gauge butterfly needle, connected to a 10 cc syringe, is utilized. This approach requires only a needle puncture through the skin followed by multiple passes through the tissue with the syringe on suction. Typically, an excellent core of testicular tissue is obtained that, in men with reasonable sperm counts, is often more than sufficient. Minimal pain and discomfort are typically reported. In cases where anesthesia is required

(i.e., for concurrent varicocele repair), or in situations of severe oligozoospermia, TESE remains an excellent option. Patients should be counseled to all risks and options with an appropriate management plan determined in conjunction with the treating reproductive endocrinologist.

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Footnote

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