

Drawbacks of the current practice

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Response to: Cunha-Filho JS. Evidence based sperm DNA fragmentation. *Transl Androl Urol* 2017;6:S527-8.

Submitted Apr 13, 2017. Accepted for publication Apr 13, 2017.

doi: 10.21037/tau.2017.04.24

View this article at: <http://dx.doi.org/10.21037/tau.2017.04.24>

Dr. Cunha-Filho, in his commentary on the practice recommendations by Agarwal *et al.* (1), described the current status of sperm DNA fragmentation (SDF) testing. He discussed the pitfalls of the current practice in using intracytoplasmic sperm injection (ICSI) in bypassing male factors on one hand, while elaborating on the current limitations of SDF testing on the other (2).

The remarkable evolution of assisted reproductive techniques (ART) in the past three decades has significantly impacted the field of clinical andrology (3). In the era of ICSI, workup of female partner remains important because she has to go through the ART procedure and pregnancy. Tremendous attention invested in improving embryo quality and pregnancy outcome after ART had led to significant advancement in recent years (4). In contrast, the role of semen analysis as the one-and-only “cornerstone” from the male perspective remained unchanged. Despite the revision of World Health Organization (WHO) criteria for semen analyses, little has been changed except more focus on strict morphology (5). Interest in sperm function tests, including hemizona assay and hamster oocyte penetration test, have disappeared as none of the tests have been widely studied clinically. The increasing use of ICSI in managing couples with severe male factors (6) renders semen analysis a screening test merely for the presence or absence of sperm in an ejaculate. The value of proper male evaluation is overlooked since ICSI possibly gives the couple a baby without explaining the nature or cause of underlying male infertility. The success and advancement of ART is obvious. However, the live birth rate utilizing ICSI as the treatment of male factor infertility is around 30% only (7).

A comprehensive male partner evaluation and correction of male infertility factors is essential in improving the outcome. The author (Dr. Cunha-Filho) brought up the important message of “over-indication of ICSI”. In fact, the use of ART for male subfertility has been recently reviewed by Cochrane database. The systematic review illustrated the fact that the use of ART in male subfertility is often not supported by evidence, the choice of ART and cutoff value of semen parameters are largely unknown. Further, most of the studies reviewed in the Cochrane review suffered from major methodological flaws (8).

Semen analysis provides information on the functional status of the genital tract in general and reflects the status of seminiferous tubules, epididymis, and accessory sex glands. It is the most widely used biomarker to predict and often taken as a surrogate measure of male reproductive potential (9). However, up to 40% of infertile men have semen parameters within the reference ranges (10,11). The ability of semen analysis in discriminating infertile from fertile men is questionable. The use of semen analysis is further hindered by the intra-individual and inter-laboratory variations. It was reported that within-subject variability over a 10-week follow up ranged from 10.3% to 26.8% and the sperm concentration showed the highest variation (12). Similarly, high inter-laboratory coefficient of variation of 34% for sperm concentration, 20% for sperm motility, and 70% for strict sperm morphology has been reported (13). Since the introduction of WHO criteria for semen analysis in 1980, the manual was revised several times and the latest version, the fifth edition came out in 2010. It is the first time semen analysis results from fathers

with known time-to-pregnancy were analyzed and the fifth percentile was proposed as the lower cutoff limits (14). The arbitrary use of 95% reference interval to define normality from semen analyses of fertile subjects was considered illogical (15). The definition of normal semen parameters has constantly changed over the last three decades. But, still, the reference values failed to satisfy clinical and statistical standards and may misclassify a men's true fertility status (16). The adoption of the lower reference limits in the 2010 WHO manual will reclassify up to 15% of men with at least one parameter below the 1999 WHO reference values as "normal" (17). Unfortunately, treatment of male infertility factors has been largely based on the often unreliable results of routine semen parameters. An infertile patient with clinical varicocele and marginally normal semen concentration may be left with no treatment until the problem become more profound with ageing. Caution must be taken when using semen parameters alone in guiding management of infertile men.

Since the introduction of SDF testing over 25 years ago, the body of literature is ever expanding. Even with some limitations as suggested by the author, significant advancement has been achieved. SDF testing has been recognized as important surrogate of male fertility by professional organizations including American Society of Reproductive Medicine (18) and the implication of abnormal SDF on natural pregnancy, ART outcome, and pregnancy loss is evident (19). Recent data also showed that sperm chromatin dispersion (SCD) and TUNEL assays have a sensitivity of 80–85% and a specificity of 85–90% in predicting natural pregnancy (20,21). It is proven that SDF tests showed predictive value independent of conventional semen parameters (22). The standardization of TdT-mediated dUTP Nick-End Labeling (TUNEL) assay is underway and high correlation between laboratories could be achieved with optimized protocol and quality control (23). The potential implication of SDF tests on treatment outcomes is illustrated by a recent studies by Bradley *et al.* and Esteves *et al.* In the former, the authors demonstrated the effectiveness of interventions, including physiological intracytoplasmic injection, intracytoplasmic morphologically selected sperm injection and testicular sperm extraction/aspiration, on live birth rate in patients with high SDF (24). In the latter, the use of testicular sperm for ICSI in preference over ejaculated sperm in men with high SDF in semen was associated with a reduced miscarriage rate and an increased live birth rate (25).

Evidence based medicine stresses on the importance of

critical review in clinical practice. The complex nature of human reproduction with multiple confounding factors poses challenges in reaching a conclusion with high-level evidence. The practice recommendations proposed by Agarwal *et al.* (1) is based on the current available evidence, though it may not be perfect and has relatively low level of evidence. In the same context, the use of ART, including ICSI, in the treatment of male subfertility remains unsupported by hard evidence and its safety on the health of offspring remains a matter of great concern. Semen analysis, though considered a cornerstone in male fertility assessment, is in itself flawed and cannot withstand the current stringent scientific appraisal. Therefore, it seems logical to welcome an emerging test that has proved itself potentially useful in acting both as an independent as well as adjunct to the current gold standard, the routine semen analysis.

Acknowledgements

None.

Footnote

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

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Cite this article as: Agarwal A, Cho CL, Majzoub A, Esteves SC. Drawbacks of the current practice. *Transl Androl Urol* 2017;6(Suppl 4):S529-S531. doi: 10.21037/tau.2017.04.24