Editorial

Sperm DNA fragmentation testing is the safe and economical way to go

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In the commentary by Drs. Carrell and Hotaling, the authors stated a vital message in the last paragraph that '…implementation of sperm DNA damage testing in the clinic with the objective of not only improving assisted reproductive technology (ART) success rates but more importantly to improve the health of the father and the offspring' (1). With the advancement of ART particularly intracytoplasmic sperm injection (ICSI), even the most severe form of male factor infertility can be bypassed. Men who remained childless previously beget their biological children with ICSI. The success of ICSI, however, may create another potential problem on the other hand as there is substantial evidence from animal studies that sperm DNA damage has a deleterious effect on offspring (2). Paternal exposure to anticancer agents in rodents can induce heritable genetic translocation and congenital malformations (3). It is also shown in mouse models that ICSI with DNA-fragmented sperm can result in premature ageing, aberrant growth, and increased incidence of tumors in the offspring (4). The relationship among paternal age, sperm DNA fragmentation (SDF), and defects in offspring in human also support the possible correlation (5). Sperm produced by ageing men exhibit impaired DNA integrity and paternal age has been linked with dominant genetic diseases (6), schizophrenia (7), and neural tube defects (8). The finding of increased chromosomal abnormalities in ICSI candidates and a higher rate of aneuploidy associated with SDF is alarming (9,10). However, the immediate advantage of ICSI overwhelms the concern of offspring's health and ICSI continues to retain the number one spot amongst many clinicians all over the world as the treatment of choice for patients with severe forms of male factor infertility. Even though, currently there is no epidemiological evidence demonstrating the association between ICSI and genetic defects; the unknown and potentially lethal long-term consequence of a pregnancy with very high levels of DNA damage remains unexplored. Most genetic defects in human may not manifest immediately but are cumulative with time. Polygenic diseases may take several generations before genetic defects became apparent clinically when it is too late to correct (11). We believe that it is still early to conclude the safety of ICSI since it was introduced directly into clinical practice merely three decades ago, without rigorous safety studies in animals.

Another important issue raised by the authors is financial incentives that may impact the management decision whether to fully work up the male or bypass male factor infertility through ICSI. A formal cost-effective study is not feasible with the current evidence given the diversity of laboratory studies and treatment strategies. But the use of SDF testing in the management of male infertility could potentially result in savings for individual couples by optimizing their ART treatment. As we know, ART procedures are costly and not without risk. While the out-of-pocket expense to cover a direct cost of one ART cycle varies considerably across countries and by insurance provider, it is estimated to be thirteen

thousand dollars in the United States (12). ART also induced indirect costs including loss of productivity, and unexpected cost of managing complications and ART failure (13). The significantly higher twin birth rate after ART (14) and greater risk of multiple gestations on both mother and fetus further compounding the cost of pre- and neonatal care (13,15). It is evident that any step that can potentially improve natural pregnancy or ART outcomes will likely to pose a financial benefit to both the couple and society. A more comprehensive workup of male factors by incorporation of SDF testing is certainly an attractive and economical option. The cost of SDF testing will probably be justified since the test results reflect treatment outcome. The appropriate and more targeted use of ART may be made possible provided that SDF testing (in conjunction with other tests) could predict ART outcomes. Selection of a technique with the highest success rate avoids the trial-and-error approach and will be a more economical way to go forward. In addition, avoiding unnecessary treatment saves time and relieves stress to the couple. SDF testing may also allow better selection of patients for varicocelectomy particularly for those with normal semen parameters and/or low-grade varicocele (16). Although SDF testing is not perfect in its current state, it is non-invasive and significantly cheaper relative to the cost of an ART cycle or surgical procedures. While the cost-effectiveness of routine application of SDF testing remains to be investigated, the testing of SDF could prove valuable in selected patient groups, as suggested in our practice recommendations (16).

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Footnote

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

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