Editorial

Development of treatment strategies in men with vulnerable sperm

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Dr. Samplaski, in her commentary, elegantly discussed different issues surrounding sperm DNA fragmentation (SDF) (1) and the author largely endorsed the practice recommendations by Agarwal *et al.* (2). Firstly, she stated the drawbacks of routine semen analysis in the evaluation of male infertility supported by data from the LIFE study (3). This was followed by discussion of the testing methodologies. The author then further elaborated on interventions for mitigating high SDF and stressed on the use of antioxidant and testicular sperm as possible treatment strategies. Additional information on deleterious effects of cryopreservation on SDF was highlighted. Finally, the author summarized towards the end in last paragraph that "plan for an intracytoplasmic sperm injection (ICSI) cycle with a fresh testicular sperm extraction (TESE)/testicular sperm aspiration (TESA)" if SDF is persistently high even after correction of all reversible factors.

In the following paragraphs, we will highlight and address two points raised by the author (I) the use of oral antioxidant, and (II) the implication of cryopreservation on SDF.

Many of the current medical therapy for male infertility rely on its antioxidant properties. It is based on the correlation between oxidative stress, and abnormal semen parameters and unexplained infertility (4,5). Although contradictory findings have been reported for various agents, several of them showed promising results. The beneficial effect of vitamin C and E have been demonstrated in a number of well conducted studies. Vitamin C is a high potency reactive oxygen species (ROS) scavenger (6). Its concentration in seminal plasma is 10-fold higher than that in serum (7). Vitamin C may have a dose-dependent effect on sperm motility (8) and seminal plasma concentrations and has been positively correlated with sperm morphology (9). Vitamin E is thought to interrupt lipid peroxidation which is mediated by ROS. Effect of vitamin E, alone or in combination with vitamin C or selenium, in improving sperm motility (10,11) and SDF (12) has been reported in randomized controlled trials. Other potentially useful antioxidants that may decrease SDF include carnitines (13), carotenoids (14), glutathione (15), and zinc (16). Many of the studies on antioxidant therapies are critiqued for small sample size, short duration, failure to perform randomized double-blinded placebo controlled studies, a lack of standardization of dose and efficacy, and the absence of pregnancy outcome as end point (17). However, the strengths of antioxidant therapies should not be overlooked. The ease of administration with oral medication or dietary supplement is attractive to patients and clinicians. Most of the agents studied did not show any kind of major adverse events. Antioxidant therapy represents a targeted therapy based on the correlations among oxidative stress, SDF and the resultant poor pregnancy outcomes (18). Correction of the underlying male infertility factor may restore fertility potential of an individual. Thereby, minimize the chance of pursuing assisted reproductive technology (ART) and sperm retrieval and avoid the associated risk and cost of treatment. The

contradictory results with regards to the benefit of oral antioxidant therapy reported in various studies may be due to the heterogeneity of patients included. Specific patients with high oxidative stress and/or SDF are more likely to response to antioxidant therapy. The application of SDF tests to identify patient subgroups most likely to benefit from therapy seems sound.

Dr. Samplaski raised the point about the deleterious effect of sperm cryopreservation on SDF (1). Indeed, it is an area of great interest but data from large studies are lacking. The negative impact of freeze/thaw on SDF has been demonstrated in some studies (19-22), while others failed to demonstrate such a relationship (23-25). The heterogeneity among the studies in procedure of cryopreservation, preparation of semen before cryostorage, testing method of SDF utilized, and more importantly, the baseline semen quality of the study subjects may explain the contradictory findings. Experience from semen processing by density gradient centrifugation illustrated that sperm from infertile patients with higher SDF are more susceptible to further damage after processing (26). Cryostorage of prepared semen by swim-up also demonstrated higher SDF, however, addition of seminal plasma to prepared sperm may have protective effect (20). In contrast, selection of sperm with better motility by discontinuous Percoll® gradient before cryopreservation showed that SDF was not affected by freeze-thaw (21). The study results demonstrate that the routine sperm preparation during IVF/ICSI cycles may exert significant impact on SDF, particularly for patients with high SDF. Therefore, the suggestion to use fresh testicular sperm with ICSI in men with elevated SDF is sound (27,28), but it is worth mentioning that no study has yet compared SDF rates in fresh versus cryopreserved testicular sperm. Finally, the issue is further complicated by the fact that supplementation of antioxidants in the process of cryopreservation may reduce ROS levels and SDF. Addition of ascorbate and catalase reduced ROS and SDF in the process of freezing/thawing (29). Supplementation of thawing medium with glutathione lead to reduced ROS and SDF, and improved fertilization capacity of frozen bull spermatozoa (30). It illustrated the importance of semen processing in the management of men with high SDF in view of high susceptibility to stress of the spermatozoa. Development of protective measures may alleviate the damage and more research in this area is essential for optimizing the care of infertile men with high SDF.

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Footnote

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

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