Editorial

Risk factors associated with sperm DNA fragmentation

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Dr. Franco (1) in his commentary in response to the practice recommendations by Agarwal *et al.* (2) provides information on several important aspects of sperm DNA fragmentation (SDF), especially the impact of paternal age, overweight and varicocele; and finally the author concluded by listing the current limitations of SDF tests.

The association between advanced paternal age and increase in SDF and the implication to pregnancy outcomes is one of the topics of our discussion. Paternal age, in contrast to female age, has become less of a concern over the last few decades ever since the introduction of assisted reproduction. Intracytoplasmic sperm injection (ICSI) has bypassed, to a certain extent, the most severe forms of male infertility. However, the relationship between paternal age and pregnancy outcome is clear. Semen parameters begin a steady decline after the age of 35 (3). Significantly more SDF is reported in men after the age of 40 (4). Time-to-pregnancy (TTP), which is an excellent measure of fertility potential, increases with an increase in male age. The "Groningen Expert Center for Kids with Obesity (GECKO) Drenthe" study from the Netherlands reported that paternal age was highly correlated with TTP on multivariate regression analysis based on data from 1,924 couples. The hazard ratio of paternal age was 1.31, 1.11 and 0.91 for age <25, 25–30 and >35 years respectively when compared to the reference category of 30–35 years of age (5). Hassan *et al.* also reported an increase in TTP in men over the age of 45. Their partner's relative risk of an increase in TTP over one and two years rose to 4.6 and 12.5 respectively (6). There were exponentially fewer infants born to fathers over 35 to 39 years of age and older compared to younger age groups. Data from the Spanish National Statistics Institute analyzing a total of 454,753 infants in year 2004 demonstrated a constant decline in male fecundity from 35 to 39 years of age at a rate of 21–23% per year up to 80 years of age (7). Dr. Franco raised another point suggesting a possible correlation between age-related SDF and mitochondrial damage which is logical. Age-associated increase in oxidative stress is the most widely accepted hypothesis that explains the association between male age and SDF (8). Oxidative stress exerts its negative effect on sperm by various mechanisms including damage to mitochondrial DNA (9). In fact, mitochondria may represent a possible source of reactive oxygen species in sperm (10). However, contrary to the author's suggestion that spermatozoal apoptosis is not correlated with ageing, there is evidence to show that oxidative stress can induce apoptosis in mature spermatozoa (11) and allow production of abnormal spermatozoa (12). These findings suggest a possible relationship between advanced paternal age and apoptosis of sperm.

Male obesity has been linked to subfecundity and a dose-response relationship between increasing body mass index and subfecundity has been reported (13). The exact underlying mechanism is unknown and SDF has been proposed as a possible mediating factor from various studies (2). While weight reduction is associated with improvements in reproductive outcomes in female (14), the effect of such treatment on male subfertility and/or SDF is less clear. Few emerging studies revealed that weight loss in severely obese men leads to improved semen parameters and reproductive hormonal profile; however, no change in SDF

measured by sperm chromatin structure assay (SCSA) was observed (15,16). Further studies are required to delineate the mechanism of obesity leading to male subfertility and the effect of weight reduction treatment.

Although larger well-designed studies are welcomed to better define the relationship between varicocele and SDF, the well-executed systematic review by Zini and Dohle provides the best evidence supporting such a relationship (17). The association is further supported by the finding that varicocele itself is associated with SDF even when fertility has not been compromised (17). The efficacy of varicocele repair in alleviating oxidative stress (18), increasing seminal antioxidants (19), and decreasing SDF (20-22) has been demonstrated. The role of antioxidants as a therapeutic alternative or adjuvant therapy in varicocele is not well established due to limited amount of data (23,24). Various sperm selection techniques have been reported to be effective in selecting spermatozoa with reduced levels of SDF (25,26), but their effect on clinical outcomes is yet to be confirmed. Current sperm selection techniques are limited by the fact that none of them could completely remove sperm with DNA damage or aneuploidies (27). Varicocelectomy, by correction of the underlying etiology, remains the only treatment option that possibly allows natural conception by restoring fertility potential. The procedure also offers the lowest risk of genetic defects to offsprings. Therefore, varicocelectomy should be the preferred treatment option in patients with varicocele and high SDF.

Lastly, we agree that current SDF testing has its own limitations. While waiting for development of new methodologies, standardization of current techniques in combination with good quality control will improve the performance of SDF tests. A recent study demonstrated that the utilization of a standardized protocol and identical bench top flow cytometry instrument for TUNEL assay offers a very high degree of accuracy between different laboratories (28). In fact, despite different SDF tests employed, the correlation between SDF and natural pregnancy/assisted reproductive technology/miscarriage has been demonstrated (29).

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Footnote

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

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