Editorial

One of the many missing links between infertility and sperm DNA fragmentation

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Dr. Harlev, in his commentary (1), largely supported the practice recommendations proposed by Agarwal *et al*. (2) and concluded by stating that sperm DNA fragmentation (SDF) testing is a step forward in the right direction. The author correctly identified the pitfalls of the current practice in the areas of unexplained male infertility (UMI) and recurrent pregnancy loss (RPL). We want to further elaborate and discuss these points.

The importance of male factor infertility is increasingly being recognized. Male factor is responsible in about 50% of infertile couples; it is the sole cause in about 20%, and is a contributory factor in 30–40% of the cases (3). Following the current protocol for evaluation of infertile male which includes history, physical examination, semen analysis and laboratory testing, a cause of infertility was identifiable in only half of the patients (4). Patients who have male infertility of unknown origin are further classified into idiopathic versus unexplained infertility based on abnormal and normal conventional semen parameters respectively (5). The drawback of the current evaluation makes targeted therapy impossible due to lack of definitive diagnosis. The advances in assisted reproductive technology (ART) dominate the treatment of infertile couples and male factor infertility is often bypassed (6). However, the overall live birth rate utilizing intracytoplasmic sperm injection (ICSI) as the treatment of male factor infertility has not exceeded 30% (7). Semen analysis represents a cornerstone in evaluation of male infertility but approximately 40% of infertile men have normal semen parameters (8). The recent changes in the 2010 World Health Organization reference values for semen analyses (9) has resulted in more infertile men falling into the category of UMI which may account for 6–27% of all infertile men (10). Many possible etiologies including immunologic and genetic causes of male infertility are often missed under the current guidelines for evaluation of male infertility. Therefore, the role of sperm function tests beyond the basic ones in identifying the underlying etiologies of UMI should be explored.

Despite the association between SDF and conventional semen parameters (11), men with high SDF may present with normal semen parameters (12). This finding forms the basis and account for the possible significance of SDF tests in providing additional information in patients with UMI. Indeed, the association of higher SDF in men with UMI has been demonstrated by various studies (13,14). Although SDF testing will not explain all cases of UMI, the incorporation of SDF in the UMI evaluation will identify patients with high sperm chromatin damage. The targeted therapeutic approach which corrects and alleviates SDF probably represents the most effective and least costly approach to restore normal fertility potential or improve ART outcomes in this group of patients.

The relationship between sperm DNA integrity and RPL is getting clearer in recent years. The role of paternal genome in RPL is not to affect implantation, but to limit the conceptus to achieve a live birth (15). Studies have

illustrated that abnormal paternal genome modifications lead to poor blastocyst development and early fetal loss (16). A late paternal effect has also been reported mainly attributed to anomalies in the organization of sperm chromatin (17). As a result, the addition of SDF testing in RPL may potentially identify the possible etiology in this group of patients which is often unknown otherwise (18). The use of SDF testing is particularly useful in men who are normozoospermic since no other useful tests are available for this group of patients. A recent study demonstrated a significantly higher SDF level in male partner of couples experiencing RPL compared to fertile controls (18.8±7.0 versus 12.8±5.3), and similar to those of infertile men. A significant positive correlation between the number of RPL events and elevated level of SDF is also reported (19). The early incorporation of SDF testing in couples with pregnancy loss should be the preferred clinical approach as the age of the couple advances after a series of pregnancies ending in miscarriages. The advanced male and female age is associated with an increase in time-to-pregnancy due to diminished ovarian reserve and sperm quality (20,21). The test result may provide the couple with opportunity to select the most appropriate ART procedure with optimal success rate.

Despite the clear benefit of SDF testing in patients with UMI and RPL, "the common belief that SDF is untreatable", as stated by Dr. Harlev, represents another obstacle for clinical application of SDF testing. In fact, the effectiveness of intervention on high SDF is supported by recent studies. Bradley *et al.* demonstrated a significantly improved blastocyst transfer outcome and single embryo transfer live birth rate in high SDF patients with interventions including sperm selection techniques and use of testicular sperm (22). A reduced miscarriage rate and increased live birth rate were also reported with the use of testicular sperm for ICSI in preference over ejaculated sperm in men with high SDF (23). In addition to sperm selection and testicular sperm retrieval, new treatment strategies including the use of oral antioxidant therapy are also extensively investigated (24).

The understanding of SDF bridges a missing link in infertility. High SDF is an underlying etiology in a subset of patients with UMI and RPL. The identification of patients with high SDF is important since high SDF is potentially treatable. After all, SDF cannot explain all UMI and RPL in infertile couples. The more we know about human reproduction, the more we appreciate the extreme complexity of the system. SDF is an important test but it is only one of the many missing links. Our knowledge of human reproduction will only be completed when the other missing links are exposed with continuous efforts of a large number of fertility specialists and researchers from all around the world.

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Footnote

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

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