Commentary

Infertility, recurrent pregnancy loss and sperm DNA fragmentation, have we found the missing link?

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Commentary on: Agarwal A, Majzoub A, Esteves SC, *et al*. Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios. Transl Androl Urol 2016;5:935-50.

Submitted Jun 04, 2017. Accepted for publication Jun 07, 2017.
doi: 10.21037/tau.2017.06.15
View this article at: http://dx.doi.org/10.21037/tau.2017.06.15

Infertility, defined as the inability to achieve pregnancy after 12 months of unprotected intercourse (1), affects approximately 15% of the couples at reproductive age (2,3). Globally, infertility rates are increasing (4) and as a consequence the use of fertility treatments for conceiving are growing. Since the birth of Louise Brown in 1978, more than 5 million children have been born by fertility treatments in the last 40 years worldwide (5). The etiology of infertility is multifactorial and may include female factors such as anovulation and mechanical issues as well as male factors, mainly abnormal sperm count or function. Yet, male infertility accounts for 30–55% of infertility among couples (6).

Defining a couple as infertile, an investigation will be initiated in order to identify the infertility cause. The investigation will follow the possible infertility etiology and involve both partners. Aside from careful history of both partners and physical examination, the basic evaluation includes assessment of the ovulatory cycle, imaging studies for a possible female mechanical factor and a semen analysis to identify male factor infertility (7). Surprisingly, to date, despite using best knowledge and utilities, only 60–70% of the infertility evaluation will yield an etiology that will explain the cause of infertility (8,9). An unacceptable portion (30–40%) of infertile couples will undergo full evaluation and remain answerless regarding the etiology of their infertility.

A similar discrepancy between the evaluation extent and the likelihood of established etiology, exists with recurrent pregnancy loss (RPL). RPL is defined as two or more failed clinical pregnancies and involves 5% of the population trying to conceive (10,11). Similar to the etiology of infertility, RPL also involves both partners with male factors playing a major role in its etiology, unlike previous thoughts (10,12). RPL evaluation will include endocrine, metabolic, thrombophilia and anatomic evaluation of the female partner and karyotype for both the male and the female (13). Alike infertility, only in 50% of the investigated couples a possible etiology will be identified (10,13).

The current status of infertility and RPL investigation reflects the limited knowledge of the possible etiologies and the resulting partial scope of evaluation. This condition is frustrating both to patients desiring to conceive as well as their caregivers. It mandates us to seek new evaluation areas and modalities. Several of the uninvestigated areas may be considered as the underlying causes for infertility and RPL, especially the genetic (including epigenetic) and chromosomal factors which are the most important under-investigated factors both in the research field and also during evaluation.

In a recent study (14), Agarwal *et al.* suggested sperm DNA fragmentation testing as a valuable tool for infertility assessment in various clinical entities. The authors detailed clinical scenarios and summarized the current knowledge for each scenario and their recommendation with regards to sperm DNA fragmentation (SDF). The need to use SDF is based on the limitation of the basic semen evaluation to offer information concerning the sperm genome integrity.

Physiologically, sperm DNA is protected from external damage by being compacted and bound to protamine (15). If some damage does occur, a repair mechanism in the oocyte cytoplasm can reverse it in most cases. However, when the damage tops the oocyte's repair ability, the fragmented DNA may alter sperm function (16) resulting either in a failed pregnancy or, if the damage is manifested in the germ line, it can lead to early childhood cancer and/or malformations (17,18). Although the cause for SDF is multifactorial, it is primarily caused by oxidative stress (19,20). In any semen sample, most of the sperm cells are morphologically abnormal, some of them due to abnormal chromatin remodeling during spermiogenesis. These cells are fated for apoptosis and are major contributors of reactive oxygen species (ROS) formation (21). ROS elevation will cause the harmful OS damage to the sperm cell including its DNA, when it will exceed the total anti-oxidant capacity (TAC).

Indeed, as expected, several *in vivo* and *in vitro* studies reported an inverse relationship between sperm SDF and both infertility (21-24) and RPL (12,25-27). Moreover, SDF was found to be inversely correlated with the success of fertility treatments including live birth rates (28). Despite this well-established observation, SDF is not widely accepted as part of the evaluation of infertility or RPL. Possible reasons for the under-use of SDF are lack of information, expensive required equipment, but most importantly, the common belief that SDF is untreatable and therefore is irrelevant. To my judgment, the main value of the recently published practice guidelines by Agarwal *et al.* (14), is to demonstrate the current evidence for the use of SDF by giving practical examples that the clinician encounters in their practice on daily basis.

The more the genomic impact on infertility and RPL is studied, better is the understanding of unexplained infertility and RPL allowing for treatment and preventative measures. It is our task and moral obligation as clinicians and caregivers to shed light on the etiology of these challenging medical conditions thus allowing more couples to fulfill their desire to conceive. The SDF is a step forward in the correct direction.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Harlev A. Infertility, recurrent pregnancy loss and sperm DNA fragmentation, have we found the missing link? Transl Androl Urol 2017;6(Suppl 4):S704-S706. doi: 10.21037/tau.2017.06.15

