Commentary

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

**Avi Harlev**

Fertility and IVF Unit, Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

*Correspondence to:* Avi Harlev. Fertility and IVF Unit, Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel. Email: harlev.avi@gmail.com.

*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.

## References

1. Practice Committee of the American Society for Reproductive Medicine. Definition of "infertility". Fertil Steril 2006;86:S228.
2. Mascarenhas MN, Flaxman SR, Boerma T, et al. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med 2012;9:e1001356.
3. Thoma ME, McLain AC, Louis JF, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril 2013;99:1324-31.e1.
4. Bushnik T, Cook JL, Yuzpe AA, et al. Estimating the prevalence of infertility in Canada. Hum Reprod 2012;27:738-46.
5. Calhaz-Jorge C, de Geyter C, Kupka MS, et al. Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. Hum Reprod 2016;31:1638-52.
6. Jungwirth A, Giwercman A, Tournaye H, et al. European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol 2012;62:324-32.
7. McLaren JF. Infertility evaluation. Obstet Gynecol Clin North Am 2012;39:453-63.
8. Gunn DD, Bates GW. Evidence-based approach to unexplained infertility: a systematic review. Fertil Steril 2016;105:1566-74.e1.
9. Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev 2012;(4):CD003357.
10. Garrido-Gimenez C, Alijotas-Reig J. Recurrent miscarriage: causes, evaluation and management. Postgrad Med J 2015;91:151-62.
11. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103-11.
12. Zidi-Jrah I, Hajlaoui A, Mougou-Zerelli S, et al. Relationship between sperm aneuploidy, sperm DNA integrity, chromatin packaging, traditional semen parameters, and recurrent pregnancy loss. Fertil Steril 2016;105:58-64.
13. Shahine L, Lathi R. Recurrent pregnancy loss: evaluation and treatment. Obstet Gynecol Clin North Am 2015;42:117-34.

 

14. 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.
15. Erenpreiss J, Spano M, Erenpreisa J, et al. Sperm chromatin structure and male fertility: biological and clinical aspects. Asian J Androl 2006;8:11-29.
16. Evenson DP, Jost LK, Marshall D, et al. Utility of the sperm chromatin structure assay as a diagnostic and prognostic tool in the human fertility clinic. Hum Reprod 1999;14:1039-49.
17. Aitken RJ, Krausz C. Oxidative stress, DNA damage and the Y chromosome. Reproduction 2001;122:497-506.
18. Hanson HA, Mayer EN, Anderson RE, et al. Risk of childhood mortality in family members of men with poor semen quality. Hum Reprod 2017;32:239-47.
19. Aitken RJ, De Iuliis GN, Finnie JM, et al. Analysis of the relationships between oxidative stress, DNA damage and sperm vitality in a patient population: development of diagnostic criteria. Hum Reprod 2010;25:2415-26.
20. Bisht S, Dada R. Oxidative stress: Major executioner in disease pathology, role in sperm DNA damage and preventive strategies. Front Biosci (Schol Ed) 2017;9:420-47.
21. Lewis SE, John Aitken R, Conner SJ, et al. The impact of sperm DNA damage in assisted conception and beyond: recent advances in diagnosis and treatment. Reprod Biomed Online. 2013;27:325-37.
22. Saleh RA, Agarwal A, Nada EA, et al. Negative effects of increased sperm DNA damage in relation to seminal oxidative stress in men with idiopathic and male factor infertility. Fertil Steril 2003;79 Suppl 3:1597-605.
23. Evenson D, Wixon R. Meta-analysis of sperm DNA fragmentation using the sperm chromatin structure assay. Reprod Biomed Online 2006;12:466-72.
24. Spano M, Bonde JP, Hjollund HI, et al. Sperm chromatin damage impairs human fertility. The Danish First Pregnancy Planner Study Team. Fertil Steril 2000;73:43-50.
25. Bareh GM, Jacoby E, Binkley P, et al. Sperm deoxyribonucleic acid fragmentation assessment in normozoospermic male partners of couples with unexplained recurrent pregnancy loss: a prospective study. Fertil Steril 2016;105:329-36.e1.
26. Ribas-Maynou J, Garcia-Peiro A, Fernandez-Encinas A, et al. Double stranded sperm DNA breaks, measured by Comet assay, are associated with unexplained recurrent miscarriage in couples without a female factor. PLoS One 2012;7:e44679.
27. Absalan F, Ghannadi A, Kazerooni M, et al. Value of sperm chromatin dispersion test in couples with unexplained recurrent abortion. J Assist Reprod Genet 2012;29:11-4.
28. Osman A, Alsomait H, Seshadri S, et al. The effect of sperm DNA fragmentation on live birth rate after IVF or ICSI: a systematic review and meta-analysis. Reprod Biomed Online 2015;30:120-7.

**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

 