Editorial

Sperm DNA fragmentation in clinical practice

Ahmad Majzoub[1], Ashok Agarwal[2], Sandro C. Esteves[3]

[1]Department of Urology, Hamad Medical Corporation, Doha, Qatar; [2]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA; [3]ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil

Correspondence to: Ahmad Majzoub. Associate Consultant, Department of Urology, Hamad Medical Corporation, Doha, Qatar Po Box 3050. Email: dr.amajzoub@gmail.com.

Response to: Benagiano G, Paoli D, Lombardo F, *et al.* DNA fragmentation and the ultimate success of a pregnancy. Transl Androl Urol 2017;6:S539-43.

Submitted Feb 11, 2017. Accepted for publication Feb 11, 2017.
doi: 10.21037/tau.2017.03.13
View this article at: http://dx.doi.org/10.21037/tau.2017.03.13

We value the comments written by Dr. Benagiano on the "Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios" (1). The author has pointed out the controversies surrounding the diagnostic potential of conventional semen parameters and tests of sperm DNA fragmentation (SDF) in cases of recurrent pregnancy loss and in predicting the outcomes of assisted reproductive techniques (ART). He concluded that SDF testing is a useful tool to assess chromatin integrity and understand the origins and mechanisms of DNA damage, however, its clinical utility is somehow hindered by the lack of well-designed studies and therefore is not widely accepted.

Conventional semen analysis is the cornerstone of male fertility evaluation. While it provides useful information on the patency of sperm production, secretions of the accessory organs, as well as ejaculation and emission, it does not predict fertility (2,3). It provides no insights into the functional potential of the spermatozoon to fertilize an ovum or to undergo the subsequent maturation processes required to achieve fertilization. Dr. Benagiano has cited previous studies which showed an association between poor sperm quality and pregnancy outcome (4-7). However, more recent studies have underscored the low diagnostic potential of poor sperm quality in predicting pregnancy outcome whether naturally or through ART. In a retrospective review of 67 patients with severe teratozoospermia (<1% normal forms), Kovac *et al.* reported natural conception in half the study patients. Moreover, 29% of men with 0% normal forms were still able to conceive (8). Likewise, previous studies reporting a significant influence of sperm morphology on the pregnancy outcome following ART (9) were questioned as some recent studies failed to replicate such an association (10,11). Studies on other semen parameters have yielded similar results too. Lemmens *et al.* (12) assessed the predictive value of sperm morphology, total progressively motile sperm count, and number of inseminated progressively motile spermatozoa in 4,251 intrauterine insemination cycles. After multivariate analysis, the authors observed that the studied parameters had a low predictive power for pregnancy. The existing drawbacks in the predictive potential of conventional semen analysis triggered the search for other tests that can be utilized in clinical practice (13). SDF testing is a good example of an an ancillary test that can aid clinicians in their efforts to improve patients' reproductive outcome. In contrast with conventional semen parameters, measures of SDF had better correlation with early embryo development and pregnancy outcomes both naturally and after ART (14,15).

Dr. Benagiano has pointed out earlier studies which detected a relationship between sperm quality and early embryo development suggesting that the sperm may have functions that extend beyond being a DNA delivery vessel. However, it is reasonable to postulate that sperm DNA defects are probably more influential on early embryo development. In fact, several studies have confirmed such an association. Simon *et al.* (14) evaluated 215 men from infertile couples undergoing ART comparing embryo development between low and high SDF groups. They detected a higher percentage of good quality embryos and a lower percentage of poor quality embryos in the low DNA

damage group (P=0.05) compared with the high DNA damage group. Implantation was also inversely related to the degree of SDF in the study population (P=0.001). Wdowiak *et al.* (15) evaluated the relationship between SDF dynamics, embryo development and pregnancy rate. In 148 couples undergoing ICSI, the SDF level (sperm chromatin dispersion test) was assessed at the day of the microinjection, as well as after 3, 6 and 12 h of incubation. The SDF level and the intensity of fragmentation were correlated with embryo growth and pregnancy outcome. The authors concluded that embryo development up until the moment of obtaining a 5-cell stage and emergence of a blastocyst, depends on the initial SDF, while the chances of pregnancy were dependent on the intensification of SDF after 12 h incubation, where a 1 unit increase in SDF, lowered the chances of pregnancy by 5.95%.

The controversy surrounding the utility of SDF in clinical practice mainly stems from the contradictory results being reported by various studies and meta-analyses, as appropriately described in Dr. Benagiano's commentary. The author cited a literature review by Lin *et al.* (16) where they investigated the relationship between SDF (measured with SCSA), high DNA stainability (HDS), and outcomes of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). After reviewing 223 couples, the authors failed to detect significant differences in IVF and ICSI fertilization rate, good embryo rate, and pregnancy rate between various levels of SDF or HDS. Moreover, higher SDF was not associated with a significant increase in abortion rate post IVF. Contrary to this, the systemic reviews and meta-analyses [reviewed by Agarwal *et al.* (1,17)] showed significant negative association between SDF levels and pregnancy rates with IVF (18,19), and a significant positive association between SDF levels and miscarriage rate after IVF and ICSI (18,20,21). Such controversies are expected in medical literature and are mainly caused by the variation in study methodologies, selection criteria, and particularly in this case, the SDF testing method being utilized. Although the American Society for Reproductive Medicine has recommended against routinely using SDF testing for the evaluation of male fertility, however, they did acknowledge the presence of a potential influence for SDF on pregnancy outcome after ART; as stated in their committee opinion (22) "*…but the effect of abnormal sperm DNA fragmentation on the value of IUI or IVF and ICSI results may be clinically informative*".

In clinical practice, it is perhaps more meaningful to look at the broader picture. SDF is not being compared to a gold standard test with superior or even equivalent clinical usefulness, in fact such a test does not exist. So from a patient and physician perspective, any test that can offers valuable information influencing the reproductive outcome deserves to be taken into consideration. It should be understood that we are not proposing the routine use of SDF during the fertility evaluation of every infertile man. Instead, we believe that in selected clinical scenarios, SDF provides beneficial information that can affect clinical decision making and consequently reproductive outcome.

Acknowledgements

None.

Footnote

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

References

1. 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.
2. Jequier AM. Semen analysis: a new manual and its application to the understanding of semen and its pathology. Asian J Androl 2010;12:11-3.
3. Esteves SC. Clinical relevance of routine semen analysis and controversies surrounding the 2010 World Health Organization criteria for semen examination. Int Braz J Urol 2014;40:443-53.
4. Furuhjelm M, Jonson B, Lagergren CG, et al. The quality of the human semen in relation to perinatal mortality. Acta Obstet Gynecol Scand 1960;39:499-505.
5. Hamamah S, Fignon A, Lansac J. The effect of male factors in repeated spontaneous abortion: lesson from in-vitro fertilization and intracytoplasmic sperm injection. Hum Reprod Update 1997;3:393-400.
6. Furuhjelm M, Jonson B, Lagergren CG. The quality of human semen in spontaneous abortion. Int J Fertil 1962;7:17-21.
7. Homonnai ZT, Paz GF, Weiss JN, et al. Relation between semen quality and fate of pregnancy: retrospective study on 534 pregnancies. Int J Androl 1980;3:574-84.
8. Kovac J, Smith R, Cajipe M, et al. Success rates of natural

conception and intra-uterine insemination in men with severely abnormal strict morphology (<1% normal forms) suggests alternatives to immediate IVF. J Urol 2014;191:e802.
9. Coetzee K, Kruge TF, Lombard CJ. Predictive value of normal sperm morphology: a structured literature review. Hum Reprod Update 1998;4:73-82.
10. Lockwood GM, Deveneau NE, Shridharani AN, et al. Isolated abnormal strict morphology is not a contraindication for intrauterine insemination. Andrology 2015;3:1088-93.
11. Hotaling JM, Smith JF, Rosen M, et al. The relationship between isolated teratozoospermia and clinical pregnancy after in vitro fertilization with or without intracytoplasmic sperm injection: a systematic review and meta-analysis. Fertil Steril 2011;95:1141-5.
12. Lemmens L, Kos S, Beijer C, et al. Predictive value of sperm morphology and progressively motile sperm count for pregnancy outcomes in intrauterine insemination. Fertil Steril 2016;105:1462-8.
13. Ko EY, Sabanegh ES Jr, Agarwal A. Male infertility testing: reactive oxygen species and antioxidant capacity. Fertil Steril 2014;102:1518-27.
14. Simon L, Murphy K, Shamsi MB, et al. Paternal influence of sperm DNA integrity on early embryonic development. Hum Reprod 2014;29:2402-12.
15. Wdowiak A, Bojar I. Relationship between pregnancy, embryo development, and sperm deoxyribonucleic acid fragmentation dynamics. Saudi J Biol Sci 2016;23:598-606.
16. Lin MH, Kuo-Kuang Lee R, Li SH, et al. Sperm chromatin structure assay parameters are not related to fertilization rates, embryo quality, and pregnancy rates in in vitro fertilization and intracytoplasmic sperm injection, but might be related to spontaneous abortion rates. Fertil Steril 2008;90:352-9.
17. Agarwal A, Cho CL, Esteves SC. Should we evaluate and treat sperm DNA fragmentation? Curr Opin Obstet Gynecol 2016;28:164-71.
18. Zini A, Sigman M. Are tests of sperm DNA damage clinically useful? Pros and cons. J Androl 2009;30:219-29.
19. 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.
20. Zini A. Are sperm chromatin and DNA defects relevant in the clinic? Syst Biol Reprod Med 2011;57:78-85.
21. Robinson L, Gallos ID, Conner SJ, et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod 2012;27:2908-17.
22. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril 2015;103:e18-25.

Cite this article as: Majzoub A, Agarwal A, Esteves SC. Sperm DNA fragmentation in clinical practice. Transl Androl Urol 2017;6(Suppl 4):S544-S546. doi: 10.21037/tau.2017.03.13

