Editorial

Live birth must be the primary reproductive endpoint in IVF/ICSI studies evaluating sperm DNA fragmentation testing

Sandro C. Esteves[1,2], Ashok Agarwal[3], Ahmad Majzoub[4]

[1]ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Campinas, SP, Brazil; [2]Division of Urology, University of Campinas (UNICAMP), Campinas, SP, Brazil; [3]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA; [4]Department of Urology, Hamad Medical Corporation, Doha, Qatar

Correspondence to: Sandro C. Esteves. ANDROFERT, Andrology and Human Reproduction Clinic, Referral Center for Male Reproduction, Av. Dr. Heitor Penteado 1464, Campinas, SP, 13075-460, Brazil. Email: s.esteves@androfert.com.br.

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We read with interest the insightful commentary by Drs. Muratori and Baldi (1) regarding the recently published practice recommendations for sperm DNA fragmentation (SDF) testing based on clinical scenarios by Agarwal *et al.* (2). The authors pointed out that there exist substantial obstacles on the road of SDF testing to be considered as an integral element of male infertility workup, including (I) the establishment of the gold standard technique for each reproductive outcome; (II) the finding of effective pharmacological treatments to decrease sperm DNA damage in vivo; and (III) establishment of correct strategies to prepare spermatozoa for ART to avoid iatrogenic damage.

Foremost among these concerns is perhaps the issue of which reproductive endpoint is more important in clinical studies evaluating SDF testing. As pointed out by Muratori and Baldi, various meta-analyses have yielded conflicting results on the predictive value of SDF with regards to reproductive outcomes of IUI, IVF, and ICSI (3-8). And as rightly noted by the authors, the use of various SDF methods and reproductive endpoints has made the comparisons arduous. However, no one will deny that live birth is the prime endpoint for the couple subjected to assisted reproductive technology (ART). Unlike clinical pregnancy, which is diagnosed by ultrasonographic visualization of one or more gestational sacs, live birth is more robust as it refers to the complete expulsion or extraction of a product of fertilization with signs of life from its mother (9). Miscarriage, on the contrary, is the spontaneous loss of a clinical pregnancy that occurs before 20 completed weeks of gestational age (9).

The influence of SDF is rarely seen peri-fertilization and during early embryonic development (10,11). However, the negative impact of SDF is usually expressed on embryonic days 3–5 (early paternal effect) and later at the implantation stage and onwards (late paternal effect) (10-12). Indeed, the current meta-analyses concur that among couples subjected to ART the risk of miscarriage is increased in those with high SDF, independent of the type of ART used (IVF or ICSI) and method of SDF testing (3-5). In a prospective clinical trial evaluating a cohort of 172 oligozoospermic men with elevated SDF (by SCD) subjected to ICSI using ejaculated and testicular sperm, we showed that while SDF was associated with an increased miscarriage risk and reduced live birth, clinical pregnancy rates were not apparently affected (11). Our findings were corroborated by Osman *et al.*, who aggregated the evidence of six studies and demonstrated that LBR was significantly reduced in couples with high SDF compared to those with low SDF (6). Although the adverse effect of SDF on ART clinical pregnancy was reported in the meta-analysis of Simon *et al.* (7), our observations suggest that live birth as an endpoint may be more revealing in ART studies involving SDF testing.

Drs. Muratori and Baldi commented that sperm chromatin structure assay (SCSA) and sperm chromatin dispersion test (SCD) have poor predictive value for ART outcome, unlike TUNEL. We feel that heterogeneity among studies included in meta-analyses is the likely reason to explain the observed results, as discussed elsewhere (13). For instance, in the recent meta-analytic study by Cissen *et al.*, the authors reported that SCSA and SCD were

associated with a poor predictive value for pregnancy in ART, unlike TUNEL (8). However, the heterogeneity in the TUNEL meta-analysis was very low (I^2 =0%) in contrast to that observed with both SCSA and SCD (I^2 >50%). This means there was less variation across the studies using TUNEL than SCD and SCSA, thus suggesting that the effect size might have been diluted by heterogeneity rather than lack of power of SDF testing. Along the same lines, only one study per SDF testing method, namely, SCSA, Comet, and TUNEL, was evaluated in the meta-analysis of Osman *et al.* (6), thus precluding firm conclusions about the superiority of any particular SDF testing method on ART outcome.

Lastly, we concede with our esteemed colleagues that SDF assays measure different aspects of SDF, but point to the fact that such aspects are interrelated to a greater or lesser extent via properties of the DNA molecule.

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Footnote

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

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