Optimizing semen parameters at the molecular level: possible avenue for improvement in assisted reproductive technology success rates?

One of the major indications for the use of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) is the presence of significantly impaired semen parameters in the male partner. These impaired parameters are typically ones that are evaluated via a routine semen analysis, such as sperm concentration and motility, as well as laboratory indicators of underlying abnormalities, such as antisperm antibodies (sperm agglutination). However, despite the ability to place a single sperm into an ovum, bypassing several potential barriers to fertility, assisted reproductive technology (ART) live birth rates are at best 30%, with this number decreasing substantially with advanced maternal age (1). This has led to efforts to identify factors that may result in early miscarriage. In this month's issue of *Fertility and Sterility*, Elsa et al. use data from 1,600 ART pregnancies to assess the value of the high DNA stainability (HDS) measure from the sperm chromatin structure assay (SCSA) as a predictor of early miscarriage (2). The authors use a cutoff threshold of 15% for HDS to predict an increased risk of miscarriage by 5% when ICSI was used. Interestingly, the authors found that elevated HDS did not predict an increased risk of miscarriage when IVF was used. The authors postulate that given the association of HDS with immature sperm, ICSI cycles may be exposed to a higher rate of immature sperm in cases of high HDS. This is in contrast to other studies that have detected a detrimental effect of sperm DNA damage (DNA fragmentation and not HDS) on clinical pregnancy rate after IVF and ICSI (3).

Although the authors touch on potential ways of considering and addressing elevated HDS in semen samples, such as using IVF instead of ICSI in cases of high HDS, they do not consider ways of modifying the actual problem: the presence of high HDS, and in other cases, high DNA fragmentation in sperm. For example, early efforts to modify DNA fragmentation index (DFI) through varicocelectomy have shown improvements in natural and ART pregnancy rates (4). Although studies associating decreased DFI with higher ART success after interventions such as varicocelectomy or retrieval of testicular sperm are increasing in number, they are all hampered by small patient populations and different outcome measures. Therefore, it is imperative that men known to have elevated DFI or HDS, or any abnormal semen parameters, be evaluated by a male infertility specialist to avoid missing an opportunity to optimize semen parameters. It will be the identification of modifiable pathology, such as varicoceles, low testosterone, and low-grade infections, in male partners in combination with large ART datasets that will allow us to begin to determine the value of attempting to optimize semen parameters such as DFI or HDS before ART.

A second limitation of the findings in this study is the inability to detect HDS in individual spermatozoa without destruction of the spermatozoa. Although an elevated percentage of HDS may be present in each semen sample—defined in this report by >15% abnormal spermatozoa in a total of 5,000 spermatozoa counted—an embryologist cannot differentiate a "normal" spermatozoon from one with HDS under the microscope when selecting sperm for ICSI. At this time the technology does not exist to detect DNA fragmentation or HDS without destroying the spermatic sample. Therefore, such sampling techniques give a very small window into the fitness of the millions of sperm not analyzed.

Elsa et al. should be commended for their large study assessing a relatively novel spermatic factor. Certainly, more studies trying to identify predictive factors for early miscarriage or repeated ICSI failure will ultimately help to increase the live birth rate for couples desperate for children (1). We hope that these authors and other authors will continue work on HDS and continue to identify the population of couples that will most benefit from HDS testing. Future work will need to determine if HDS testing should be regularly performed for couples with recurrent pregnancy loss or recurrent IVF/ICSI failures, or even all newcomers to ART. The authors' findings are certainly an exciting new spermatic parameter to consider, although additional studies are required to know when testing for HDS is appropriate as well as what methods can be used by male infertility specialists to improve the rate of HDS in couples presenting with this elevated parameter.

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