Commentary

Sperm DNA fragmentation: indication and uses

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If you really think about it, the microscopic portion of conventional sperm analysis relies on the same principles of light microscopy that have been present since Antony van Leeuwenhoek first saw sperm cells in the 17th century. Cell counts, motility, and cellular beauty (based on our idea of an ideal sperm) guide us on a daily basis.

Sperm DNA fragmentation testing, represents our best attempt at getting beyond the limits of light microscopy (especially with the wane of sperm functional tests in the era of IVF-ICSI), and that is indicated by the explosion of research into the topic. Agarwal and co-authors (1) expertly update us on the biological rationale and the strengths and weaknesses in the myriad of sperm DNA fragmentation tests that are available. They further go on to review common clinical scenarios and discuss evidenced-based implications of sperm DNA fragmentation testing in those situations.

They provide a wonderful framework for which to consider SDF testing in clinical practice in a number of scenarios:

(I) SDF testing may help better select varicocelectomy candidates among men with borderline or normal semen analysis parameters;

(II) SDF may provide a possible explanation in couples with unexplained infertility or recurrent pregnancy loss or intrauterine insemination failures;

(III) SDF may help provide prognostic information in couples that have failed IVF or IVF/ICSI. Additionally, high SDF may be a reason to consider using testicular sperm rather than ejaculated sperm with IVF;

(IV) Abnormal SDF results may help those with environmental exposure, occupational exposure or lifestyle risks factors because any abnormality may reinforce the importance of lifestyle modification and exposure minimization.

These are all important points and certainly conventional semen analysis parameters are able to shed little light into these scenarios. Yet despite the benefits of SDF testing, the application of SDF testing in these scenarios is not without its limitations, and certainly some of the benefits discussed above can clearly be debated.

Specifically in scenario 1 (men with clinical varicoceles and normal or borderline semen analyses), the critical assumption is that SDF provides more information because SDF represents an independent marker of sperm quality independent of conventional semen analysis parameters. This is an area of active research, and the data is mixed at best (2).

In scenario 2 (with unexplained infertility or recurrent pregnancy loss or insemination failures), providing any kind of information for unexplained infertility or in recurrent pregnancy loss or IUI failures represents an improvement in care. However, while varicocelectomy studies have shown improvements in SDF after varicocelectomy, the amount of improvement is moderate at best (3). As such if there is poor SDF, do we really have good tools to lower it a significant amount? In cases with normal SDF or mildly elevated SDF, certainly varicocelectomy may help in those patients with clinically palpable varicoceles. In cases with severe SDF, varicocelectomy may not help enough, and couples who undergo varicocelectomy but don't get pregnant have been found to have higher SDF (4).

In scenario 3 (couples who have failed IVF using

ejaculated sperm with high SDF), the use of testicular sperm represents an exciting area that merits further research. The limited data we have on this topic seems to suggest better outcomes (5), but more rigorous studies are needed before we expose all men in this scenario to the risks of sperm retrieval procedures.

In scenario 4 (patients with lifestyle or occupational toxic exposures), while it would be nice to give patients more information to compel them to avoid occupational or lifestyle exposures, my common sense approach to these exposures is to ask them to try and avoid these exposures as much as they can no matter what. Smoking and obesity are two areas the authors mention. As a physician in a large health system that believes in prevention for overall better health, I would argue (as any physician would), that losing weight and smoking cessation are good for overall health in addition to the fertility benefits and should be encouraged no matter what the SDF results. I tell my patients that even beyond fertility, they should work on this for their overall health to be able to be around to raise their future children. For occupational exposures, again avoidance of exposures to chemicals would be optimal, but of course avoidance may mean a different job or limitations on the job. However, workers should always use the personal protective devices offered and minimize exposure to chemicals. So for lifestyle counseling, I'm not sure an additional test would change my counseling. In light of a normal SDF result, would any fertility doctor encourage a patient to smoke?

Certainly, the authors have raised excellent points about uses of SDF testing which may identify an issue for those patients who otherwise would be "idiopathic". And we do have the ability to moderately improve SDF in men. But in my mind the biggest clinical limitation of this testing remains whom we should test and its inability to change many couples clinical course.

The fact that SDF correlates well with natural pregnancy and IUI pregnancy (and even conventional IVF) rates are encouraging, but the limitation is that the correlation breaks down with the application of IVF-ICSI. In my practice, I recommend those with very poor SDF go straight to IVF-ICSI. If the couple is able to heed that advice they should undergo testing. Many couples though say they will still do IUI 3 times and only go onto IVF if they fail IUI. If that is the case, I don't see how SDF testing changes their clinical course. As such, SDF testing remains a useful adjunct for the right population. However, recognition and proper application of this test are essential, and these work expert authors have written a wonderful piece every clinician should read.

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Footnote

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