Rethinking the role of sperm morphology in clinical practice

Sperm morphology has endured as a cornerstone of routine semen analysis for decades. While there has been significant evolution in the definition of "normal" sperm morphology over time, the World Health Organization continues to consider morphology as an essential component of routine semen analysis. Indeed, the landmark study from Guzick et al. (1) found that abnormal morphology was associated with the highest risk of infertility among all individual semen parameters (concentration, motility, and morphology). However, several subsequent studies have demonstrated little to no association between morphology and pregnancy across a wide range of clinical settings, including natural conception, intrauterine insemination, and in vitro fertilization (2–4). This may be, in part, due to the fairly subjective nature of sperm morphology and high variability in its measurement—even the most experienced laboratories can fail to provide consistent morphology measurements, as both interobserver and intersample variability have been demonstrated to be consistently high.

The current study adds to the body of literature characterizing the challenges of morphology assessment and reinforces the pitfalls of measuring sperm morphology.

In a secondary analysis of the Males, Antioxidants, and Infertility trial, Baker et al. (5) compared morphological assessments on the same semen sample performed by the local Reproductive Medicine Network laboratory and subsequently by the core laboratory for the trial. These are world-class laboratories at high-volume centers with a wealth of experience. Amazingly, there was no overall correlation between the percent normal sperm (PNS) values at the local sites and the core. More importantly, when dichotomizing PNS according to clinically useful cutoffs (4% or 0), there was extremely poor interobserver agreement between the local sites and the core ($\kappa = 0.05$ and 0.15, respectively). That is, in the context of a rigorous trial and laboratory protocols, these expert laboratories could not even agree on the complete absence of normal morphological sperm in a specimen. How can we rely on sperm morphology to guide our clinical management of couples with subfertility if the best of laboratories cannot agree on even the most basic morphological assessment?

Beyond this inconsistency and lack of reproducibility in morphological assessment, there is a growing body of evidence showing limited associations between teratozoospermia and clinical outcomes. Even men with 0% normal morphology have a significant chance of conceiving without assisted reproductive technology (2). In addition, for couples who do proceed to intrauterine insemination or in vitro fertilization, sperm morphology is not associated with clinical pregnancy (3, 4). As such, the finding of teratozoospermia is rarely prognostic or clinically useful and instead serves to increase patient anxiety regarding an abnormal value that likely has little clinical impact.

Given the increasingly clear limitations in measurement and clinical utility of sperm morphology, we must reconsider the role of morphology in routine semen analysis and clinical practice. Perhaps we should treat morphology strictly as a screening tool for field defects in spermatogenesis that are incompatible with natural conception, such as globozoospermia, macrozoospermia, and pinhead morphology. Morphological assessments could transition from quantitative (PNS) to qualitative (presence or absence of globozoospermia), which would distill the elements of morphology that we know are certain to impact a couple's reproductive care and outcome. Alternatively, we need to develop more advanced tools, whether through new technology or artificial intelligence, to improve the accuracy and precision of morphology assessment and/or detect morphological subtleties that are invisible to the human eye. Only then can we begin once again to determine whether morphology, in a new and improved iteration, is truly important for clinical decision-making.

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REFERENCES

1. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388–93.
2. Kovac JR, Smith RP, Cajipe M, Lamb DJ, Lipshultz LI. Men with a complete absence of normal sperm morphology exhibit high rates of success without assisted reproduction. Asian J Androl 2017;19:39–42.
3. Kohn TP, Kohn JR, Ramasamy R. Effect of sperm morphology on pregnancy success via intrauterine insemination: a systematic review and meta-analysis. J Urol 2018;199:812–22.
4. Hotaling JM, Smith JF, Rosen M, Muller CH, Walsh TJ. 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.
5. Baker KC, Steiner AZ, Hansen KR, Barnhart KT, Cedars MI, Legro RS, et al. Poor reproducibility of percentage of normally shaped sperm using WHO5 strict grading criteria. F S Rep. In press.