

# An Assessment of New Sperm Tests for Male Infertility

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The routine semen analysis, although used for more than 50 years, fails to accurately distinguish between fertile and infertile men. As a consequence, many tests of sperm function (TSF) have been developed. This review discusses both older and newer diagnostic TSF. It outlines the principles underlying each assay and reviews aggregate clinical data to determine its current relevance and utility. It concludes that the relevance of many older TSF is questionable, with the wide acceptance of intracytoplasmic sperm injection (ICSI). Newer TSF have the potential to deliver more clinically relevant information but require more extensive study to better understand their predictive role in the ICSI era. UROLOGY 77: 1027–1034, 2011. © 2011 Elsevier Inc. All rights reserved.

In addition to the medical history and physical examination, the conventional semen analysis has been an essential laboratory test for the evaluation of male fertility for at least 50 years. However, the idea that fertility can be defined by threshold values of semen parameters is a concept that is fundamentally flawed.<sup>1</sup> Although not a true measure of fertility, the semen analysis, if abnormal, suggests that the probability of achieving fertility is lower than normal.<sup>2</sup> Because of biological variability, two semen analyses are generally needed, performed with two to three days of sexual abstinence and evaluated in a standardized fashion.<sup>2</sup> Recognized normal values for semen parameters are given in Table 1 in agreement with the latest recommendations by the World Health Organization (WHO).<sup>2</sup> Traditionally, (except for the latest WHO recommendations), these references are derived by expert consensus and not by prospective clinical trials and thus their true relationship to male fertility is unclear. In addition, the definition of what constitutes “normal” semen parameters is constantly challenged. A meta-analysis of 29 US studies of semen quality from 9612 fertile, or presumably fertile, men suggested that a sperm concentration of 98 million/mL is normal.<sup>3</sup> Although sperm motility is considered the “best” predictor of fertility, normal sperm motility ranges from 53% to 62%.<sup>4</sup> Thus, simply deriving “normal” semen parameters has been a prohibitively lengthy and inconclusive process to date.

Finally, other biological variables affect the clinical utility of the semen analysis. In addition to wide intra-individual variation, seasonal<sup>5</sup> and geographic variation<sup>4</sup> further complicate the performance of the semen analysis as a fertility measure. As examples, within-subject, in-

terejaculate coefficients of variation for sperm concentration and motility are estimated at 44.7% and 15% in one study.<sup>1</sup> Thus, even with excellent quality control, wide biological variation in semen quality profoundly challenges the notion that the conventional semen analysis can accurately assess male fertility.

## OLDER ADJUNCTIVE SPERM TESTS

Because of the need to more precisely characterize normal fertile semen, adjunctive semen testing has become popular (Figure 1). The concept behind developing adjunctive sperm tests is that the functional competence of sperm matters for fertility. Although such testing has fallen out of favor in the last decade with the rise of intracytoplasmic sperm injection (ICSI), the idea that not all sperm used with ICSI are the same has reignited interest in adjunctive sperm testing.

### Sperm Morphology

One of the oldest adjunctive sperm tests is the formal evaluation of sperm shape, termed *morphologic assessment*.<sup>6</sup> Several descriptive systems exist to evaluate morphology, and within each system, sperm are designated normal or abnormal based on specific criteria. It is believed that sperm morphology may correlate with a man's fertility potential as reflected by in vitro fertilization (IVF) success in case cohort studies.<sup>7</sup> More recently, however, the ability of sperm morphology to distinguish candidates who are at risk of failing IVF has been called into question.<sup>8</sup> In addition, test reliability and reproducibility are low and normal biological variation may be high, all of which complicate and reduce the performance of sperm morphology as a diagnostic test.

### Sperm Penetration Assay (SPA)

This bioassay, first described by Yanagimachi and colleagues in 1976, examines the ability of sperm to pene-

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