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Concepts to Consider When Choosing an Assay to Predict Potentially Fertile Sperm

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Short Commentary

The primary goal of semen analysis is to determine whether or not an ejaculate has a sufficient number of potentially fertile sperm to achieve the desired outcome of conception. Given the significant advancements in Assisted Reproductive Technology (ART) in developed countries where IVF and ICSI are widely available to address male-factor fertility concerns, then what is the remaining utility of semen analysis? For many physicians and patients, assays to evaluate the fertilization potential of semen continue to be essential as a gateway to specialists who can perform the aforementioned ART procedures. Most initial semen analysis requests are from gynecologists, general practitioners, family practitioners, and urologists who wish to advise their patients regarding their fertility status. If male-factor infertility is detected, only then can these physicians refer patients to reproductive endocrinologists, often due to insurance considerations. Infertility is also a global concern, and many doctors and patients worldwide do not have access to the advanced technologies that are available in wealthy, developed nations. For these patients, knowing the fertility status of the man is necessary in order to overcome infertility.

It has become clear that the traditional diagnostic methodology applied to the ejaculate is inadequate when it comes to assessing the fertility status of a male patient [1,2], as a man with an abnormal semen analysis may be fertile. Conversely, a normal semen analysis does not ensure that the sperm are functionally capable of fertilizing an egg. Fertility is contingent upon the sperm's ability to penetrate and migrate through the cervical mucus, reach the ampullae of the fallopian tubes, and fertilize the oocytes. The sperm must then be able to undergo capacitation and the acrosome reaction; penetrate the zona pellucida and fuse with the oocyte; and undergo nucleus decondensation, fusing with the female chromatin materials to form a full complement of chromosomes. The idea of absolute fertility is therefore problematic, because a spermatozoon is a complex cell that becomes infertile when any one of a number of biochemical or morphological parameters is disturbed. Normalcy of a single parameter – or even several parameters – does not guarantee that the other parameters are normal. This may be the reason why none of the sperm quality assays, including the newer, more inventive methods developed in the last few decades, have proven to be highly effective predictors of potentially fertile sperm.

This is further compounded by frequently observed inconsistencies in ejaculate quality, even between samples from the same individual. The fertilization potential of a single ejaculate is dependent on the age of the sperm in the caudal epididymis, the extent of sexual stimulation, and the duration of sexual abstinence prior to ejaculation.

The ejaculate comprises sperm that were produced at different times, leading to different ages of sperm stored in the caudal epididymis. In other words, the pool of sperm in the caudal epididymis is composed of sperm of many different ages. In studies on rabbits, investigators have observed a decrease in the percentage of motile, normal-morphology, live and fertile sperm when retained in the caudal epididymis for many days

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[3]. Similarly, ejaculates fractionated via silica wool column filtration revealed a gradual but significant decrease in the motility percentage, functional membrane integrity, acrosin content, and hamster oocyte penetration potential from the first fraction to the subsequent second and third fractions [4]. These findings together provide evidence to support the concept that the sperm quality inconsistencies in any given ejaculate may be due in part to variation in the ages of the sperm.

An individual's psychological state and extent of arousal are also important factors that can influence semen quantity and quality tremendously. Studies have demonstrated that particularly satisfactory and enthusiastic sexual stimulation yields better ejaculate quality than that obtained through masturbation alone. An ejaculate collected at home with the aid of a patient's spouse can therefore be of higher quality than one produced by self-masturbation. Similarly, any discomfort or anxiety associated with semen procurement in a clinical setting can affect the volume and overall quality of semen collected. The relative levels and types of arousal, comfort and stimulation all affect the ejaculate quality.

Studies have also demonstrated that the duration of sexual abstinence prior to semen procurement can profoundly influence semen quality. Many millions of sperm are continuously produced every day; and, in the absence of ejaculation, they accumulate in the caudal epididymis and are not completely emptied when subsequently ejaculated. As a result, a good majority of the accumulated sperm remains and are emitted during subsequent ejaculations. Although a longer period of abstinence will therefore result in a higher quantity of sperm in the ejaculate, the average age of those sperm will be higher, which may compromise the overall quality. These highly variable factors may explain the frequently observed intra-individual variation in ejaculate composition; and, therefore, the results of the routine semen analysis.

It is clear from these findings that high sperm concentration and count are not always indicators that a given ejaculate has a high fertilization potential. On the other hand, based on available literature, Wang and Swerdloff [2] suggest that when sperm concentration or total sperm count is low, male fecundity is likely decreased. These observations highlight the complexity inherent in determining male-factor fertility, stressing the need for newer, more nuanced tests.

Given the fact that ejaculate quality is highly variable, it is difficult to develop and validate an assay that can consistently and accurately identify potential fertility. Ideally, fertilizing potential may be directly appraised by incubation of sperm with oocytes under natural reproductive or controlled laboratory conditions. Such a procedure, of course, is difficult, if not impossible, to be implemented during routine evaluations. Barratt et al. [5] strongly recommend assessing a combination of several sperm parameters to predict potential fertility, rather than a single sperm parameter. This recommendation may not be completely valid, because normalcy of several sperm parameters does not guarantee that the remaining, unmeasured parameters are normal.

On the other hand, if limits are established for a new or presently known sperm characteristics and functional parameters such that, below or above the established values, it is more than 95% certain that spermatozoa cannot fertilize, then it will be possible to declare a person infertile with a high degree of certainty, if any of these assay results fall within the infertile range. If no assay value is abnormal, no definitive statement can be made regarding the fertility status of the individual, because it is always possible that an unmeasured parameter is defective. If such a cutoff cannot be found for a given parameter, or is so low or high that very few individuals would fall into the range, then the test is of no diagnostic use. This concept is also applicable to assays developed for oocyte quality and embryo competence. Even using this stringent process of assessment, misdiagnosis would be possible in 5% of the evaluations.

A test that can simultaneously assess the normalcy of most if not all of the known sperm characteristics of individual spermatozoa or a population of sperm is an ideal to aspire to; however, such a test at present does not exist. Ultimately, it may be possible to perform multifactorial analyses on the data for a variety of different sperm parameters, so that a combination of factors can be taken into consideration when assessing male-factor fertility. However, we are still many years away from being able to do so appropriately. Such analysis should wait until a more comprehensive evaluation of the functional activity of the sperm organelles is possible.

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