

Evaluation of sperm damage: beyond the World Health Organization criteria

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Current knowledge of the molecular basis of male infertility that is associated with oxidative stress, apoptosis, and chromatin damage calls for changes in the laboratory assessment of the fertility potential of semen samples. (Fertil Steril® 2007; ■: ■–■. ©2007 by American Society for Reproductive Medicine.)

For more than 25 years, the World Health Organization (WHO) has served to provide a standardized approach to the assessment of the fertility potential of semen samples. These standards are concerned with measurable parameters such as the physical properties of an ejaculate; estimation of the count of its cellular content, be that according to sperm or leukocytes; and the grading of sperm morphology and motility. The WHO's laboratory manual also provides a standardized approach for examining anti-sperm antibodies in seminal plasma and in the preovulatory mucus that is produced by the uterine cervix. The adoption of these standards worldwide has been enhanced through local schemes of quality control measures that lead to andrology laboratory accreditation and certification. The first andrology laboratory manual published by the WHO in 1981 was the culmination of clinical experience and research from the previous 80 years (1). In its successive editions, the WHO manual offered stricter criteria in assessing parameters of interest. As a result, the cutoff values for sperm count, motility, and normal morphology that were thought to be compatible with normal male fertility were modified (2, 3).

The resounding success of the WHO criteria has been met in recent years by a call for further scrutiny of sperm quality. Restricting sperm assessment to the traditional parameters of sperm count, motility, and morphology has highlighted numerous concerns, including the following. First, sperm count, motility, and normal morphology may fluctuate, and their assessment can be very subjective and prone to intra-observer and interobserver variability (4). Second, although the traditional semen analysis maintains its central role in the assessment of male fertility potential, this often is inadequate to provide a definitive diagnosis of the cause of male infertility (5). Conventional semen analysis per se cannot cover the

diverse array of biological properties that the spermatozoon expresses as a highly specialized cell, such as the presence of sperm apoptosis and chromatin fragmentation (6, 7). As a result, many infertile couples with no detectable abnormalities are labeled with the clinically vague diagnosis of unexplained infertility.

Third, the predictive power of the cutoff values of the traditional sperm parameters is not absolute, because there is some degree of overlap between fertile and infertile male populations. Further modification of these cutoff points has been advocated as a way to enhance the predictive power of the standard semen analysis. However, this approach may change the degree of overlap of values for fertile and infertile men without addressing the need to establish a concrete diagnosis of the underlying cause of male infertility.

Fourth, we now have a better understanding of the impact of processes such as sperm capacitation and acrosome reaction (8), sperm oxidative stress (OS) (9), and apoptosis (10) on sperm-egg interaction and on the fertilizing ability of sperm, both in vivo and in vitro. The assessment of these aspects of sperm function is beyond the current edition of the WHO manual, an issue that needs to be addressed to improve our diagnostic and therapeutic approaches to male infertility.

Last but not least, numerous studies in the literature have demonstrated that semen quality is declining and that the incidence of testicular cancers is increasing (11, 12). These observations have been shown to be associated with increased sperm chromatin damage. On a wider scale, it recently has been suggested that electromagnetic wave and radiofrequency radiation may induce OS and DNA damage in the male germline, potentially affecting male fertility (13). However, this remains controversial (14), and its impact on the incidence of male infertility in future generations has not even been considered. During in vivo reproduction, natural selection against infertile men limits their opportunity to pass on an infertility trait to offspring, with only rare exceptions. However, some assisted reproduction technologies bypass this natural

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selection process, leading to the possibility that an abnormal spermatozoon will be selected to fertilize the oocyte.

There is a significant consensus that sperm OS; apoptosis; and DNA damage that is induced by disease, lifestyle issues, and environmental factors are implicated in the pathogenesis of male infertility. In view of this current understanding and the availability of the required laboratory techniques to test for evidence of sperm OS, apoptosis, and DNA fragmentation (9, 10, 15, 16), additional assessment of sperm damage beyond the WHO criteria has become feasible. This may serve to provide a definitive diagnosis of the underlying causes of what thus far has been labeled as “idiopathic” and “unexplained infertility”. This may also identify the group of men who, through techniques such as intracytoplasmic sperm injection, may perpetually propagate their genetic complement that is linked to male infertility. The strategies required to achieve this goal should encompass an effort to address the lack of standardization of the laboratory techniques that are required to test for sperm OS, apoptosis, and chromatin damage. It is conceivable that the next task of the WHO is to facilitate the endeavor to determine the most appropriate laboratory tests and the associated standards to achieve this goal. This will involve inviting stakeholders and recognized authorities in the field to formulate a consensus view. Unless the WHO seeks rigid standardization of these tests, the mistakes of the past will be repeated. In doing so, the WHO could provide a standardized two-level approach for male fertility assessment. Level 1 should be adequately served by the criteria and standards included in its current manual, with the objective of offering an initial screening for men presenting within an infertile relationship. Level 2 testing would have the objective of offering a definitive diagnosis for men with abnormal findings in level 1 testing. This also will uncover potential causes of infertility in couples who are labeled as having unexplained infertility in the level 1 assessment. Level 2 testing is also desirable for those who are offered intracytoplasmic sperm injection. Such assessments yield information not only on the fertilizing capacity of human spermatozoa but also on their ability to support normal embryonic development. It would appear that the time is ripe for this leap forward in male fertility assessment.

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