



## RE: Clinical relevance of routine semen analysis and controversies surrounding the 2010 World Health Organization criteria for semen examination

Sandro C. Esteves<sup>1</sup>

<sup>1</sup>ANDROFERT, Andrology & Human Reproduction Clinic, Campinas, SP, Brazil

*Int Braz J Urol.* 2014; 40: 443-53

*To the editor,*

Dr. Sandro Esteves and colleagues, from Brazil, performed on page xx at this issue of the International Braz J Urol an elegant review that discuss how the new World Health Organization (WHO) criteria for seminal parameters could affect the clinical management of men presenting with male infertility. The authors emphasized the factors that limit the use of seminal parameters as a surrogate for male fertility and also propose a template to be used for semen analysis reports to allow a better interpretation for clinicians.

Biological proof of male sterility is only present in cases of azoospermia or in the presence of a complete lack of sperm motility. Since such cases of male sterility are uncommon, clinicians presume to obtain a clear indication of a man's fertilizing potential from semen analysis. That would be finding a cutoff value in order to determine which number of sperm count, motility or morphology could better differentiate fertile patients from subfertile patients. The precise statistical test to find this "magical" number would be through a generation of a receiver operating characteristic curve which examined various cutoff values to determine one with high sensitivity, specificity and accuracy that would be superior in differentiating both populations. Unfortunately, the application of this test may be relevant in relation to certain clinical tests including levels of sodium or potassium in serum, but are unsuitable for seminal parameters because there is a significant overlapping distribution in the sperm characteristics between fertile and subfertile populations (1, 2).

The definition of "normal" semen quality has changed over time (3, 4). The 2010 WHO guidelines have reduced the reference limits for seminal parameters, in the sense that the 'normal' reference range was defined as the one that covers 95% of a population (5). The current suggested reference values fail to satisfy clinical and statistical standards and pose the risk of misclassifying a subject's true fertility status (2). Moreover, the introduction of these new values to the clinical practice is likely to result in a reclassification of many infertile couples (6). As an example, those couples previously classified as having male factor infertility with sperm parameters greater than the new reference limits, but less than the previous values, probably, will now be diagnosed as having unexplained infertility. Moreover, as the newest lower reference limits are even lower than the previous reference values, clinicians will likely be faced with an increased number of men presenting with treatable causes of infertility, as varicocele, and semen parameters within the "normal reference" values. Since the recommendation for varicocele treatment has been based on the results of routine seminal parameters, an important question has now risen: Should we perform a varicocele repair for an infertile

men presenting with clinical varicocele and sperm concentration of 16 million/ml? According to the current guidelines for varicocele management, treatment should be offered to men with clinical varicocele in the presence of abnormal semen analyses. The application of the new reference values might consider ineligible for treatment many men previous submitted to varicocelectomy, as many previous abnormal semen analysis will now be considered “normal”. Therefore, these patients will not only be left without treatment but also will not even be referred for male infertility evaluation.

It is tempting to suggest that the lower reference limits of semen parameters, as proposed by the most recently WHO manual, are part of gradual declines in sperm count extensively reported over the past decades, and that these changes might be responsible for a possible decline in the fertility rates in the industrialized world (7). The stated drop in semen quality is a matter of great interest since it has been associated with an adverse trend for an increased incidence of other urologic male disorders including testis cancer and undescended testis. The observed effects have been linked to lifestyle and environmental exposures to endocrine disruptors. However, currently, there is no scientific truth of a causative role for endocrine disruptors in the temporal decline of sperm production as well as there is no enough evidence to confirm a worldwide decline in sperm counts or other semen parameters (8). As a result, one must exercise caution when concluding that the newly proposed lowered WHO reference values can be justified by the suggested decline in global sperm quality, because it is more probable that such differences are instead related to a methodological bias created by different ways of generating reference values (6).

The 2010 WHO manual still retains the nomenclature that is regularly applied by some to describe deviations from reference semen values. The use of words rather than numbers such as oligozoospermia, asthenozoospermia and teratozoospermia, do not allowed for an exactly knowledge were the result is according to the complete reference interval. I perfectly agree with the authors that such terminology should be abandoned. Seminal parameters results should be reported only numerically to allow an appropriate individual interpretation. In addition, the proposal of a new template for seminal analysis report including the full reference interval is an excellent suggestion allowing a better understanding for clinicians as well as patients when interpreting seminal parameters numbers by comparing the specimen results with the entire reference group distribution.

In conclusion, the current WHO guidelines for normal semen quality should be used with caution. We must keep in mind that the interpretation of the reference ranges for semen parameters requires an understanding that seminal parameters within the 95% reference interval do not guarantee fertility nor do values outside those limits necessarily indicate male infertility (5). Although, the 2010 WHO manual aimed to provide evidence-based thresholds that would aid clinicians in estimating the relative fertility of a given patient, seminal parameters absolutely do not allow the definitive classification of patients into fertile or infertile.

## REFERENCES

1. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al. National Cooperative Reproductive Medicine Network. Sperm morphology, motility, and concentration in fertile and infertile men. *N Engl J Med*. 2001;345:1388-93.
2. Nallella KP, Sharma RK, Aziz N, Agarwal A. Significance of sperm characteristics in the evaluation of male infertility. *Fertil Steril*. 2006;85:629-34.
3. WHO. World Health Organization: WHO Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. Cambridge: Cambridge University Press, 1992.
4. WHO. World Health Organization: WHO Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. New York: Cambridge University Press, 1999.

5. WHO. World Health Organization: WHO Laboratory manual for the examination and processing of human semen - 5th ed. Geneva: WHO Press, 2010.
6. Esteves SC, Zini A, Aziz N, Alvarez JG, Sabanegh ES Jr, Agarwal A. Critical appraisal of World Health Organization's new reference values for human semen characteristics and effect on diagnosis and treatment of subfertile men. *Urology*. 2012;79:16-22.
7. Bromwich P, Cohen J, Stewart I, Walker A. Decline in sperm counts: an artefact of changed reference range of "normal"? *BMJ*. 1994;309:19-22.
8. Cocuzza M, Esteves SC. Shedding light on the controversy surrounding the temporal decline in human sperm counts: a systematic review. *ScientificWorldJournal*. 2014;2014:365691.

*Marcello Cocuzza, MD*  
*Section Editor, Infertility*  
*Internacional Braz J Urol*  
*Department of Urology, University of São Paulo,*  
*SP, Brazil, HCFMUSP*  
*Rua Adma Jafet, 50 151/152*  
*São Paulo, SP, 01308-050, Brasil*  
*FAX: + 55 11 3256-9511*  
*E-mail: mcocuzza@uol.com.br*