

Letters to the Editor

Reference limits: limited references in laboratories worldwide

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Dear Editor

The newly revised World Health Organization (WHO) semen analysis manual provides the lower reference limits of semen parameters based on “the raw data from between about 400 and 1 900 semen samples, from recent fathers in eight countries on three continents”: Australia, Europe and North America [1]. The other continents, Asia, Africa, and South America, and most regions of the above three continents, such as southern Europe, were not represented in the raw data used to generate the reference limits. To my knowledge, no valid and well-controlled data regarding semen from men whose partners had conceived within the preceding 12 months have been collected from these unrepresented regions. Profound comments on this regard have been made and published in the Special Issue in *Asian Journal of Andrology* on “Semen analysis in 21st Century Medicine” in Issue 1 in 2010 [2–5]. In this letter, I would like to present some of my views and suggestions on reference limits of semen parameters.

Previous data from screened and general populations showed that there are obvious differences in semen quality between continents [6], countries [7] and even different areas in the same country [6, 8, 9]. Some of the studies also revealed temporal differences [10]. The underlying reasons were unclear. Temporal and geographical differences in semen quality might reflect differences in environmental factors and, ethnic or

genetic backgrounds or a combination of factors. Although more studies are needed to understand the full biological significance of these differences, a study by Joffe *et al.* [11] suggested that they might be related to differences in fecundity. The observation that spermatogenesis in Asian men appears to be more susceptible to suppression by steroidal contraceptives than that in Caucasian men has been proposed to be related to ethnic differences in testicular structure (smaller testes, reduced number and function of Sertoli cells and reduced daily sperm production) and spermatogenic potential [12]. Differences in reproductive endocrinology between Asian men and Caucasian men have also been suggested [13]. It is possible that more sperm are produced in individuals in some ethnic populations, resulting in higher fecundity. Even in cases of similar levels of sperm production, it is possible that higher fecundity can be achieved by sperm that are better able to fertilise the egg or, conversely, by eggs that are easier to be fertilized. As a result, the fifth centiles (with 95% confidence intervals) from the raw data derived from a population with higher sperm production might be higher. These values would be lower in a population with sperm or eggs that result in higher fecundity. Therefore, it seems highly reasonable to suppose that the reference limits in men whose partners were pregnant within the last 12 months vary among countries with different ethnic backgrounds. Great caution should be taken when using the WHO manual’s reference limits

for populations in the smaller represented regions of the world as the basis for conclusions regarding populations in the larger unrepresented regions, especially those with different ethnic backgrounds, with the aim of distinguishing fertile and subfertile populations.

All versions of the WHO semen analysis manual have recommended that, because of the limitations of the manual's reference data, laboratories consider preparing their own reference ranges. Not only regional but also potential ethnic differences in semen quality should be considered when establishing the reference ranges appropriate for a particular area.

The revised WHO manual provides more detailed and effective quality-control procedures than the previous versions. These improved procedures can reduce methodological laboratory biases. The WHO-recommended procedures should be regarded as a basis for efficient comparison of results from laboratories in different regions. A recent survey [14] showed that in most laboratories in China, there was considerable deviation from the standard procedures recommended in the WHO manual. Further studies on geographical and ethnic differences, based on the techniques recommended in the WHO manual, are warranted before the reference limits can be applied in China and other unrepresented regions.

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