Re: World Health Organization Guideline for the Prevention, Diagnosis, and Treatment of Infertility (2025)—Concern about the diagnosis and treatment of male factor infertility: the position of the Italian Society of Andrology and Sexual Medicine, the Italian Society of Endocrinology, and the Italian Society of Fertility and Sterility and Reproductive Medicine

We read with interest the first World Health Organization (WHO) Guideline for the Prevention, Diagnosis and Treatment of Infertility (2025) (1). This guideline represents an important effort to systematize global fertility care and to expand access to evidence-based diagnostic and therapeutic strategies. Its ambition is particularly laudable, given the increasing social, demographic, and clinical relevance of infertility worldwide. After careful review, we believe that some aspects of male factor infertility could be more fully addressed in future updates of the guideline, as the current document places greater emphasis on the female partner, which may inadvertently contribute to a less balanced representation of couple infertility, despite the fact that male factors contribute in at least half of the cases. In particular, the diagnostic and therapeutic approaches to male factor infertility appear simplified, potentially overlooking recent scientific evidence, while emphasizing aspects that currently play a limited role in clinical management. Addressing these points may represent an opportunity to further enhance the scientific robustness and equity of the guideline.

The guideline itself acknowledges that male factors contribute wholly or in part to approximately 50% of all infertility cases globally. Nonetheless, the diagnostic section devoted to the male partner is almost entirely limited to semen analysis and its repetition. Such simplification is difficult to reconcile with modern andrological standards and also with the last edition of the WHO manual for semen analysis interpretation, which explicitly states that semen analysis cannot diagnose infertility (and cannot give information about the cause and the pathophysiologic mechanisms involved), cannot distinguish fertile from infertile men, and has little prognostic value for the reproductive potential of the couple. This discrepancy risks inadvertently reinforcing a misleading dichotomy, in which semen parameters are given the diagnostic authority they do not possess. Indeed, semen analysis just represents the first diagnostic test in male partners of infertile couples and should only suggest the subsequent diagnostic process, which needs to be completed in a personalized manner using all the diagnostic tools that andrologists have at hand: infectious disease analysis on seminal fluid, scrotal and transrectal ultrasound imaging, hormonal analyses, genetic tests, etc. Results of semen examination below the WHO reference values (5th percentile) do not automatically mean that the problem in that couple resides in the male, and results above the reference limits do not always mean that the male partner of the couple is undoubtedly fertile (2). Therefore, it is quite singular that the present guideline recommends ending the diagnostic process when semen parameters are within the WHO reference ranges, and recommends referring to male infertility specialist, without any other indication, when semen parameters are outside these ranges. The information derived from semen analysis is only partial, even considering the extreme intraindividual variability and the intrinsic variability linked to a laboratory analysis that is performed manually.

In this sense, several recent studies have emphasized that semen analysis should be viewed as the starting point of male evaluation rather than its conclusion (3). The male reproductive system is influenced by endocrine, genetic, infectious, environmental, metabolic, lifestyle/behavioral, and systemic factors, and an adequate workup requires a broad andrological approach that includes different tests along with a detailed history and physical examination exploring comorbidities, exposures, and risk factors (4). Indeed, the results of semen analysis can be interpreted only when combined with the clinical, biochemical, hormonal, imaging, and genetic data. The WHO guideline omits all of these components from its core diagnostic recommendations. As a result, its framework risks reinforcing the widespread clinical practice, repeatedly criticized in the literature, of underestimating the male partner or evaluating him with insufficient thoroughness. Notably, although the guideline provides detailed diagnostic algorithms for female infertility, the diagnostic pathway for the male partner appears more limited, and future iterations might benefit from a more structured and etiologically oriented classification. The number of recommendations for diagnosing infertility is also inconceivably skewed toward female factors: nine for female factors (3 for ovulatory dysfunction, 1 for tubal disease, 5 for uterine cavity abnormalities), just two for males, referred only when a semen test should be repeated. This approach could lead to misclassification of

male factors, and above all to an overdiagnosis of "idiopathic infertility," which is often simply the consequence of an incomplete diagnostic pathway. Indeed, when a comprehensive evaluation of the male partner of the infertile couple is performed, an etiological category can be identified in the vast majority of men previously labeled as idiopathic (5). Moreover, male infertility has emerged as a sentinel marker of general male health, being associated with higher risk of prevalent and incident cardiometabolic disease, malignancies, endocrine dysfunction, and increased long-term morbidity and mortality (3). Highlighting this aspect could reinforce the broader public health relevance of male infertility assessment.

A parallel limitation emerges in the therapeutic section of the guideline. Indeed, although extensive and nuanced recommendations for female factor infertility are provided, treatment of male factor infertility is almost entirely reduced to varicocele repair. Varicocele could be a cause of male infertility, but it represents only a minority of the cases, as reported in the guideline itself. The only other therapeutic approach mentioned is antioxidant supplementation, whose use is not recommended as evidence-based treatment by the guideline correctly. At the end, no treatment is suggested for male factor infertility. This fuels the obsolete and bizarre idea that there is no treatment for male factor infertility and the bad habit of recommending assisted reproduction as the first therapeutic approach (when the primary aim of reproductive specialists and infertile couples should be to restore, if possible, natural fertility). Obviously, if the diagnostic pathway is insufficient, there can be no therapeutic strategy.

In this context, future guideline updates could benefit from addressing pharmacological treatments with established clinical evidence, particularly hormonal therapies that have a long history of clinical use and recommendations/suggestions in major international guidelines (4). In this setting, one omission is particularly striking. Over the past 3 decades, an extensive body of literature, including more than twenty clinical trials and multiple meta-analyses, has evaluated follicle-stimulating hormone therapy in men with normogonadotropic oligoasthenoteratozoospermia or idiopathic infertility. The collective evidence shows improvements in sperm concentration and total sperm count, as well as increased natural and assisted reproductive technology pregnancy rates. Acknowledging this body of evidence could help clarify that selected subgroups of men may benefit from medical therapy, provided that an adequate diagnostic workup is performed.

The guideline similarly does not address treatment of male-specific endocrine and metabolic disorders (e.g., hypogonadism, hyperprolactinemia, thyroid dysfunction, overweight/obesity, metabolic syndrome, diabetes mellitus), management of genital tract infections and inflammations, or evidence-based approaches to idiopathic infertility. While the WHO guideline appropriately calls for cost-effective, feasible, and equity-oriented interventions, these aims are not incompatible with a more complete overview of valid therapeutic options. This omission could reinforce the misconception that the only possible treatment concerns women and male infertility is not treatable except through assisted reproductive technology.

Although we realize that, as admitted by the investigators, this is the first WHO guideline and subsequent editions will be developed in an effort to cover all the aspects of infertility, we must underline that a serious conceptual problem still exists. Indeed, infertility should be conceptualized as a matter of a couple, and the diagnostic and therapeutic process should proceed in parallel for both partners. Overevaluating the woman while underevaluating the man creates asymmetry in blame, burden, and treatment pathways, and contributes to sociocultural misconceptions that disproportionately affect women. A comprehensive male evaluation is thus not only clinically appropriate but essential for gender equality, an objective the WHO guideline explicitly promotes.

Finally, we must condemn the lack of recommendations regarding the sexual health of infertile patients. Too often, in real clinical practice, we observe that people who visit infertility clinics are treated by staff who are uneducated and untrained in sexual medicine, despite the fact that sexual intercourse is still the primary means of reproduction in our species. For example, despite the extensive coverage given in the guidelines to female infertility factors, a major and common condition like vaginismus is not even mentioned. Furthermore, reiterating the WHO's more than commendable position on the right to reproductive health of LGBT+ people would also have been appropriate here.

In conclusion, although the WHO guideline represents an important foundation for global infertility care, future revisions could further enhance its impact by providing a more comprehensive and balanced representation of male factor infertility. We respectfully suggest expanding diagnostic recommendations to include a complete andrological workup, acknowledging male infertility as a marker of general health, and incorporating evidence-based medical therapies alongside surgical management. Such refinements would help ensure that the guideline continues to evolve in line with contemporary evidence and provides equitable guidance for the care of infertile couples worldwide.

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