ORIGINAL ARTICLE: ANDROLOGY

Validation of the American Society for Reproductive Medicine guidelines/recommendations in white European men presenting for couple's infertility

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Objective: To retrospectively validate the American Society for Reproductive Medicine (ASRM) guidelines/recommendations concerning endocrine evaluation in a cohort of white European men presenting for couple's infertility.
Design: Retrospective study.
Setting: Academic reproductive medicine outpatient clinic.
Patient(s): Cohort of 1,056 consecutive infertile men (noninterracial infertile couples).
Intervention(s): Testicular volume was assessed with a Prader orchidometer. Serum hormones were measured (8–10 A.M.) in all cases. Hypogonadism was defined as total T < 3 ng/mL, according to the Endocrine Society definition. Semen analysis values were assessed based on the 2010 World Health Organisation reference criteria.
Main Outcome Measure(s): ASRM indications for endocrine assessment in infertile men (sperm concentration <10 million/mL, impaired sexual function, and other clinical findings suggesting a specific endocrinopathy) were used to predict hypogonadism in our cohort. Moreover, a clinically user-friendly three-item nomogram was developed to predict hypogonadism and was compared to the ASRM guidelines assessment.
Result(s): Biochemical hypogonadism was diagnosed in 156 (14.8%) men. Overall, 669 (63.4%) patients would have necessitated total T assessment according to the ASRM criteria; of these, only 119 (17.8%) were actually hypogonadal according to the Endocrine Society classification criteria. Conversely, 37 (23.7%) out of 156 patients with biochemical hypogonadism would have been overlooked. The overall predictive accuracy, sensitivity, and specificity of the ASRM guidelines was 58%, 76%, and 39%, respectively. Our nomogram was not reliable enough to predict hypogonadism, despite demonstrating a significantly higher predictive accuracy (68%) than the ASRM guidelines.
Conclusion(s): The current findings show that the ASRM guidelines/recommendations for male infertility workup may not be suitable for application in white European infertile men. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Male infertility, guidelines, semen parameters, hormones, testosterone

Discuss: You can discuss this article with its authors and with other ASRM members at

Male factor infertility still remains a poorly understood disease; although extensively studied, up to 30%–45% of cases remain unexplained (1). This number is significant considering the fact that outcomes in infertility management are often rather frustrating and that nonidiopathic causes might be treatable (1). Therefore, a proper diagnostic workup would be advantageous in terms of both etiologic assessment and, above all, subsequent effective treatment (2). Several attempts have been made to achieve standardized and evidence-based criteria for the evaluation of the infertile male. Nevertheless, available recommendations

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and guidelines are of poor support to date. If, on one hand, international guidelines substantially agree concerning semen evaluation in the infertile man, things somehow become less clear when dealing with hormone determination. Considering the European Association of Urology (EAU) guidelines (1), despite suggesting a hormone assessment for infertile men with primary testicular failure, no clear indications are provided regarding when/how hormone measures should be used for patient assessment. The American Society of Reproductive Medicine (ASRM) also lacks guidelines related to this issue but published a 2015 updated Committee Opinion about diagnostic evaluation of infertile men (3). This document clearly states that the identification and treatment of correctable conditions will improve the male partner's fertility and allow conception to be achieved naturally. The ASRM recommendations for endocrine evaluation of infertile men are straightforward and include an initial evaluation with total T (tT) and FSH for men with [1] abnormal semen parameters, particularly when the sperm concentration is <10 million/mL; [2] impaired sexual function; or [3] other clinical findings that suggest a specific endocrinopathy. Further workup (second early morning measurement of tT, serum free T, LH, and PRL) remains indicated whenever tT is found to be <3 ng/mL. To the best of our current knowledge, neither these recommendations nor the EAU guidelines have been externally validated.

Considering these aspects, a strong need emerges for shared and reliable evidence-based support for the basic management of the infertile male in everyday real-life clinical practice. Thus, the aim of our study was to retrospectively validate the ASRM recommendations for endocrine evaluation in the infertile man in a cohort of white European men presenting at the same academic outpatient clinic for couple's infertility and to develop a novel nomogram capable of predicting tT levels <3 ng/mL.

MATERIALS AND METHODS

Patients

The analyses of this cross-sectional study were based on a cohort of 1,056 consecutive white European men assessed at a single academic center for primary couple's infertility (noninterracial infertile couples only) between September 2005 and January 2015. Patients were enrolled if they were ≥ 18 year old and had either male factor infertility or mixed factor infertility. Male factor infertility was defined after a comprehensive diagnostic evaluation of the female partners. According to the World Health Organisation (WHO) criteria, infertility is defined as not conceiving a pregnancy after at least 12 months of unprotected intercourse regardless of whether or not a pregnancy ultimately occurred (4). Secondary infertility was defined as the inability to conceive after a previous pregnancy (4).

During the office visit, patients were assessed by means of a physical examination and a thorough self-reported medical history including age, comorbidities, and previous drug prescriptions. Comorbidities were then scored with the Charlson Comorbidity Index (CCI) (5). We used the International Classification of Diseases, 9th revision, because its coding algorithms were used to define the 17 comorbidities that constitute the most widely used CCI score. For the specific purpose of the analysis, CCI was categorized as 0, 1, ≥ 2. Body mass index (BMI), defined as weight in kilograms by height in square meters, was measured for each patient. Testes volume was assessed using a Prader orchidometer. Patients underwent at least two consecutive semen analyses, both showing at least one parameter below standard values for normal semen parameters according to the WHO criteria (6).

A complete hormone profile was requested and obtained for every patient as per our academic department internal guidelines; according to these, venous blood samples were drawn from each patient between 7 A.M. and 11 A.M. after an overnight fast. FSH and LH were measured using a heterogeneous competitive magnetic separation assay (Bayer Immuno 1 System, Bayer). Inhibin B (InhB) was measured with an enzyme-linked immunosorbent assay (Beckman Coulter AMH Gen II ELISA). Total T levels were measured via a direct chemiluminescence immunoassay (ADVIA Centaur; Siemens Medical Solutions Diagnostics), and sex hormone–binding globulin levels were measured via a solid-phase chemiluminescent immunometric assay on Immulite 2000 (Medical Systems SpA). Calculated free testosterone was derived from the Vermeulen formula (7). Hypogonadism was defined as tT $<$ 3 ng/mL (8). The same laboratory was used for all patients.

All the above listed data were then collected in our prospectively maintained institutional database. Data collection followed the principles outlined in the Declaration of Helsinki; all patients had signed an informed consent agreeing to deliver their own anonymous information for future studies. The study was approved by our local ethics committee.

Statistical Analyses

Statistical analysis consisted of different steps. First, descriptive statistics focused on frequencies and proportions for categorical variables. Medians and interquartile (IQ) ranges were reported for continuously coded variables. The chi-square test and Mann-Whitney *U*-test were used to compare proportions and medians, respectively. Second, the ASRM recommendations of [1] abnormal semen parameters, particularly when the sperm concentration is <10 million/mL; [2] impaired sexual function (assessed through the IIEF questionnaire (9), the Q3 International Society for Sexual Medicine 2014 definition of premature ejaculation (10), and the previous study by Salonia et al. (11)); or [3] other clinical findings that suggest a specific endocrinopathy (this last point was implemented mainly focusing on the Endocrine Society clinical practice guidelines (8); the presence of those clinical signs was evaluated in each patient by a single expert with competence in both urology and endocrinology [A.S.]) were retrospectively validated in our population, evaluating their accuracy as for the area under the curve (AUC) estimates. Third, univariable (UVA) and multivariable (MVA) logistic regression models predicting the presence of biochemical hypogonadism were fitted, including age, BMI, mean testicular size, and azoospermia as covariates. Mean testicular size was chosen neither to underestimate nor to overstate the impact of varicocele that