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# Analysis of semen parameters in male referrals: impact of reference limits, stratification by fertility categories, predictors of change, and comparison of normal semen parameters in subfertile couples

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**Objective:** To [1] determine the impact of semen reference limits on referrals for male fertility evaluations, [2] analyze the stratification of subjects based on published "normal" thresholds, [3] analyze the odds of changing fertility categories during serial tests and thereby the potential impact of inherent variability of semen parameters on referrals, and [4] determine variable(s) predictive of change.
**Design:** Retrospective chart review.
**Setting:** Academic referral center for male fertility.
**Patient(s):** New encounters in a male fertility clinic over a 5-year period that straddles the publication of World Health Organization (WHO) 2010 reference values.
**Intervention(s):** None.
**Main Outcome Measure(s):** Demographic and clinical variables, semen values, and fertility categories as follows: BE (below WHO 2010 criteria), BTWN (above WHO 2010 but below WHO 1999 criteria), and N (above WHO 1999 criteria).
**Result(s):** A total of 82.3% of initial semen tests were categorized as BE, and the predominance of this category was unchanged by publication of the WHO 2010 criteria. Men with initial semen analysis categorized as BTWN or N represented 16.2% and 1.5% of the referral population, respectively. Subjects initially categorized as BTWN were more likely to change fertility categories, and overwhelmingly this migration was downward. Analysis of normal individual semen parameters revealed statistically worse mean concentration and motility when at least one other parameter fell below the WHO 2010 criteria.
**Conclusion(s):** Men with semen results above reference criteria are underrepresented, indicating that reference limits influence referral patterns for male fertility evaluations. Normal mean concentration and motility were lower in men with at least one other individual semen parameter below the 2010 criteria, suggesting global dysfunction in spermatogenesis. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
**Key Words:** Semen analysis, infertility male, referral and consultation

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Semen analysis is an indispensable tool during the evaluation of the infertile couple, and its interpretation has a profound influence on the workup, treatment, and outcomes reporting for infertility. Yet the decision to refer may rest upon providers with limited training in male reproduction and little more to guide them than laboratory values for the "normal" semen analysis. Interpretation of semen analyses is further muddled by the inherent variability of semen parameters and the lack of threshold values that consistently differentiate fertile from subfertile couples (1–8). Furthermore, there are

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legitimate reservations about using the World Health Organization 2010 (WHO 2010) reference limits as criteria for a male fertility evaluation. First, the values are derived from a population of fertile men and therefore do not represent the population in question: couples failing to achieve pregnancy. Second, the cutoff values for normal were set at the fifth percentile of the population distribution—a threshold that has no known correlation with fecundity. As eloquently stated by Joffe, "[the WHO 2010 reference limit] implies that 5% of [fertile] men have fewer than 15 million spermatozoa per ml of semen, but does not specify what portion of men with fewer than 15 million spermatozoa per ml are fertile …" (9).

Although semen results constitute only one criterion for an evaluation, experience at our institution indicated that couples with normal semen analyses were underrepresented in our population, which suggested that adoption of stricter reference limits would further curtail access to a comprehensive fertility evaluation (10, 11). Furthermore, we wondered what percentage of couples would oscillate between "normal" and "abnormal" semen results during serial semen testing and therefore might be denied a referral because of the inherent variability of their semen parameters. In 2012 Murray et al. published a focused, retrospective examination of the semen values of 685 infertile men seen at two fertility centers and reported that the application of WHO 2010 criteria resulted in 15% of their study population being recategorized as "fertile" (12). Additional details about the demographics and stratification of the study population, variability in semen values, and prevalence of associated diagnoses and fertility-directed treatment were not provided, however, leaving key questions about the potential impact of WHO 2010 reference limits on referral patterns for male fertility unanswered.

Our objectives were to [1] determine the impact of semen reference limits on referrals for male fertility evaluations, [2] analyze the stratification of subjects based on WHO 2010 and WHO 1999 normal threshold values, [3] analyze the odds of a subject changing fertility categories during serial semen testing and thereby determine the potential impact of inherent variability of semen parameters, and [4] determine the clinical and laboratory parameters, if any, that are predictive of changing fertility categories. We feel this study will inform the debate regarding the application of normal semen values to subfertile couples and determine whether reproductive specialists are reaching the appropriate patient population.

## MATERIAL AND METHODS

### Subject Recruitment, Exclusion Criteria, Data Set Creation, and Assurance of Data Integrity

The Institutional Review Board approved this study. All new encounters at the male fertility center between January 1, 2006, through December 31, 2011, were retrieved from the electronic medical record. The demographics; semen analyses; ICD9 codes encompassing varicocele, hypogonadism, and cryptorchidism; and prescription history for androgens, aromatase inhibitors, selective estrogen receptor modulators, and gonadotropins (i.e., medications known to impact sperm production) were retrieved for the candidate pool from July 1, 2005, through June 30, 2012 (corresponding to the 6 months before and after the dates of subject retrieval). Subjects who completed at least one semen analysis from 180 days before to 90 days after their initial evaluation were considered potential study candidates.

Institutional surgical logs were reviewed, and subjects who underwent vasectomy reversal were excluded from the study group. Chart review was performed on all subjects with a history of medications known to alter sperm production (see above) or an ICD9 code encompassing hypogonadism. Subjects on these medications up to 1 year before presentation were excluded from the initial study group. Subjects in the study group were excluded from further analysis after varicocelectomy or the initiation of medications known to impact sperm production.

Chart review was conducted for semen parameters with values out of the expected range, and, when appropriate, these values were corrected. Corrected values constituted less than 0.5% of all possible data points. Concentration was designated as 0 when the presence of sperm was detected only after pelleting the sample. This designation was necessary in 7% of all semen tests.

### Specimen Collection and Semen Testing

All semen tests were performed at one of two andrology laboratories certified by the American Association of Bioanalysts or the College of American Pathologists and employing a total of 10 dedicated andrology technicians over the study period. Subjects received written and/or verbal instructions to abstain from ejaculation for 3–7 days before specimen submission. Semen specimens were collected by masturbation into clean collection cups and allowed to liquefy, and then the following variables were manually determined in accordance with the methods outlined in the WHO fourth edition: volume, sperm concentration, total motility (herein referred to as motility), % normal forms by Tyberg/strict morphology (herein referred to as strict morphology), and leukocyte concentration.

### Categorization of Semen Results

Semen results were categorized on three distinct levels (parameter, overall test, and cumulative categories). A visual representation is provided in Supplemental Figure 1.

**Parameter categorization.** Individual semen parameters were assigned to one of three categories based on the thresholds for normal semen values published in WHO 1999 (13) and WHO 2010 (14) as follows: BE (i.e., below) for values below WHO 2010 lower threshold limits, BTWN (i.e., between) for values at or above WHO 2010 lower threshold limits but below WHO 1999 lower threshold limits, and N (i.e., normal) for values at or above WHO 1999 lower threshold limits (see Supplemental Table 1). Parameters with blank values were not categorized and constituted 6% of all possible data points.

**Overall test categorization.** Each semen test was assigned to one of three overall test categories based on the following strategy: BE if at least one parameter fell below WHO 2010