The effect of the new 2010 World Health Organization criteria for semen analyses on male infertility

Katie S. Murray, D.O., Andrew James, M.D., James B. McGeady, M.D., Michael L. Reed, Ph.D., Wayne W. Kuang, M.D., and Ajay K. Nangia, M.B.B.S.

Objective: To quantify the effect of the new 2010 World Health Organization (WHO) semen analysis reference values on reclassifying previous semen analysis parameters and definition of patients with male factor infertility.

Design: A multi-institutional retrospective chart review.

Setting: University and private male infertility clinics.

Patient(s): Men referred for infertility evaluation.

Intervention(s): Comparison of semen analysis values based on 2010 versus 1999 reference criteria.

Main Outcome Measure(s): Quantification of the change based on individual sperm parameters and as a whole.

Result(s): A total of 184 men had at least two semen analyses; 13 (7%), 17 (9.2%), 34 (18.4%), and 29 (15.7%) patients changed classification to being at or above the reference values by the 2010 criteria for semen volume, sperm concentration, motility, and morphology, respectively. A total of 501 men had one semen analysis on file; 40 (7.9%), 31 (6.2%), 50 (9.9%), and 74 (19.3%) would change classification for volume, concentration, motility, and morphology, respectively. Overall, 103 patients (15.1%) who had one or more parameter below the reference value on the original analysis were converted to having all parameters at or above the 2010 reference values.

Conclusion(s): The 2010 reference values result in some infertile men being reclassified as fertile if status is based on semen analysis alone. This may lead to fewer men being referred for proper infertility evaluation or treatment. (Fertil Steril® 2012;98:1428–31. ©2012 by American Society for Reproductive Medicine.)

Key Words: Andrology, semen analysis, WHO criteria, male infertility

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Infertility affects more than 6 million couples in the United States (1). Male factor is involved in nearly one-half of these cases. The current definition of infertility is defined by the American Society for Reproductive Medicine as the inability to achieve a pregnancy through natural means after 1 year (2). The definition for male factor infertility is less clear. Most organizations and providers base the diagnosis on an “abnormal” semen analysis alone without knowing or investigating the responsible etiology/mechanism. Semen analysis becomes the sole marker responsible for many of the male/couple referrals to infertility clinics nationwide.

With assisted reproductive technology (ART) becoming a more feasible option for couples, more men are requiring sophisticated interpretation of their semen analysis. If any component of the analysis appears “abnormal,” these men are often referred to a male infertility clinic for further evaluation. As such, this relies on creation of reference threshold values for semen analysis, which the World Health Organization (WHO) has been attempting over the past 30 years. There are no true “fertile” or “normal” cutoffs for semen parameters. The only way that quantitative parameter terminology can be used is to state a value as “above” or “below” minimum reference values. Since 1987 the WHO has published five editions of the “WHO Manual for the Examination of Human Semen and Sperm–Cervical Mucus Interaction.” The most recent publication of the 2010 criteria have included lower reference values than the 1999 manual, for the first time based on...
a population study of fertile men (time to pregnancy of partner ≤ 1 year) across 14 countries (3). The authors of the study developing the new WHO criteria state that the development and application of clear reference values should help to reduce the incidence of misdiagnosis of fertility problems and improve clinical care (3). However, the controversy over the significance of a cutoff value defining fertile from nonfertile men without knowledge of the overall clinical history is a concern (3, 4). The values created in the 2010 WHO study were from 4,500 fertile men. The WHO did not examine semen analyses from infertile men and therefore did not define men as infertile if they were below the one-sided 95% confidence interval of fertile men. The value of semen analysis parameters themselves has been questioned with other functional sperm abnormalities potentially evident that are independent from the current measured parameters (5, 6). Unfortunately for now, most clinical laboratories rely on the basic testing for semen analysis and cutoff reference values. Providers still rely on them to determine plan of care. Abnormal semen parameters also serve to define male factor infertility, and as such remain the method of reporting male factor to the Society for Assisted Reproductive Technology (SART) and the Centers for Disease Control and subsequent analysis of outcomes from ART (7, 8). For this reason, it is important to try to validate the effect of the new 2010 WHO semen analysis parameters in terms of the potential paradigm shift if any on clinical practice—from potential referrals for further investigation to methods of treatment.

The objective of the present study was to determine the number of men who would change classification from “infertile” to “fertile” based on semen analysis alone according to the change proposed by the 2010 WHO criteria.

MATERIALS AND METHODS

Institutional Review Board approval was obtained from both centers. A retrospective chart review was performed of patients who presented with infertility for > 1 year or were found to have abnormal semen analysis parameters on evaluation. The core parameters of the analysis evaluated in the study were semen volume, sperm concentration, sperm motility, and sperm morphology. These parameters were all reviewed and compared with the new 2010 WHO reference values separately and as an entire semen analysis. Based on this information, we determined which semen analyses would change from being below the reference values by the previous 1999 definitions to at or above the reference values based on the 2010 criteria. Single semen analyses were studied separately. If there were two or more semen analysis per patient, the average of the parameters was used. The 2010 WHO sperm reference values for these parameters included a semen volume of 1.5 mL, sperm concentration of 15 million/mL, sperm total motility of 40%, and sperm with a normal morphology of 4% (Kruger criteria). This is in contrast to the 1999 WHO parameters for semen volume of ≥ 2.0, sperm concentration of ≥ 20 million/mL, sperm motility of ≥ 50%, and ≥ 14% normal morphology of sperm. We determined the percentage of patients that would change criteria based on each individual parameter and then the overall percentage of changed semen analyses.

RESULTS

Semen analyses of men from the University of Kansas and the University of New Mexico Southwest Fertility Center for Men were reviewed over a 2-year period. Of all the semen analyses on file in the two infertility clinics, 184 patients had a least two analyses and 501 a single semen analysis.

Of the 184 patients with multiple semen analyses, 13 (7%), 17 (9.2%), 34 (18.4%), and 29 (15.7%) patients would change classification to being at or above the reference values by the 2010 criteria for semen volume, sperm concentration, sperm motility, and sperm morphology, respectively. Of the men that had one semen analysis on file, 40 (7.9%), 31 (6.2%), 50 (9.9%), and 97 (19.3%) would change classification for semen volume, sperm concentration, motility, and morphology, respectively (Table 1).

Based on all of the parameters that were reviewed (semen volume, sperm concentration, sperm motility, and sperm morphology), 103 (15.1%) of those with at least one parameter below the reference value based on old criteria would be converted to being considered “normal” by having all parameters at or above the 2010 WHO semen analysis lower reference values.

DISCUSSION

Fifteen percent of couples are subfertile, and in one-half of these a male factor is involved (1, 9). This definition is made either by diagnosis of a known cause of male infertility or based solely on semen analyses in idiopathic cases. For this reason, either an arbitrary or scientifically derived definition of a “fertile” threshold has been used. Since before 1980, there has been a push to standardize male infertility investigations and male contraceptive studies. The

<table>
<thead>
<tr>
<th>Semen analysis parameter</th>
<th>No. of patients with multiple semen analyses (averaged) recategorized</th>
<th>No. of patients with single semen analysis recategorized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume</td>
<td>13 (7)</td>
<td>40 (7.9)</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>17 (9.2)</td>
<td>31 (6.2)</td>
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<tr>
<td>Sperm motility</td>
<td>34 (18.4)</td>
<td>50 (9.9)</td>
</tr>
<tr>
<td>Sperm morphology</td>
<td>29 (15.7)</td>
<td>97 (19.3)</td>
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WHO published their first edition of the WHO semen analysis manual in 1980, and it has undergone five editions, the latest in 2010. This manual has been a worldwide standard for laboratory semen analysis methods (10). The changes in semen analysis reference value parameters have been based on increasing evidence regarding values for fertility. A study from Belgium in 1997 documented a need for change in semen testing interpretation. It compared a fertile and subfertile population to define values for different semen parameters. It concluded that cutoff values and ranges for fertility needed to be reassessed by the World Health Organization (9). A similar study from Singapore in 1998 compared semen parameters of fertile males to the WHO recommended normal values from 1992. It showed that only 20% of fertile men had sperm morphology within the normal range as defined at that time (11). The predictive power of cutoff values of the traditional sperm parameters is not absolute with a significant degree of overlap between fertile and subfertile (4, 12). The standardization of semen analysis is very difficult for many reasons, including the use of subjective techniques with no standards for comparison, technical training, and reluctance to change (13). The problem is perpetuated by the fact that we continue to erroneously use cutoffs/reference values as a definition of “fertility” or “normal.” This is a problem because functional dysfunction of sperm can also exist in spite of normal parameters and needs to be considered although it is difficult to evaluate (5, 6). The only way that a parameter can be referred to is as “above” or “below” a reference value; we currently have to accept the limitations of this definition. The clinical history and timeline remain the most important aspects that define infertility for the couple.

The WHO, for the first time in the 2010 fifth edition, of the manual studied 4,500 fertile men in 14 countries and established the lower limit for fertility based on the 5th percentile seen with the cohort (3). Unlike many other test parameters that follow a normalized curve, with the upper and lower 2.5% being outside the “normal” limits, semen parameters have no upper limit, and it is well understood that many patients above the 5th percentile are still fertile. The new WHO criteria actually lowered all of the semen analysis values. The effect of these changes on defining male infertility diagnosis, referrals to an infertility specialist, and treatment remains unclear and was the purpose of the present study.

Our study showed that up to 15% of men who would have been considered to be infertile according to one or more abnormal semen parameters by the 1999 WHO criteria guidelines alone would now be considered to be at or above the minimum reference values for fertile men. This is interesting, because the changes from the 1999 to 2010 reference parameters are only 0.5 mL in volume, 5 million/mL in concentration, 10% in total motility, and 10% in morphology. What at first seems like a relatively small change has a large potential impact. This might actually result in these men being classified as fertile by many providers, especially in idiopathic cases where the only feature may be the semen analysis to make a decision on male factor. This will affect reporting data for research or even demographics and outcomes e.g., to SART. This may mislead and misrepresent the definition of male infertility and under represent the cause and subsequent work-up of infertility in a couple. Our study highlights the problem of semen analysis alone being a marker of male infertility and the effect of any change in reference values. All providers should of course still acknowledge that the timeline of >1 year defines infertility and overrides any semen analysis, whether abnormal or normal. Providers should also appreciate that male factor may also still exist even with normal semen parameters, especially if functional sperm abnormalities are present. This issue remains largely poorly known/undefined, and therefore under evaluated/investigated, with male factor being underestimated (6). Medical disease associated with male infertility may also be missed with fewer men potentially being defined as infertile by the new reference values. Kolettis and Sabanegh (14) found that 6% of infertile men were found to have significant medical pathology detected by the infertility work-up. A controversy is also whether fewer men will be referred for ART if more are defined as “normal.” This is unlikely, because the criteria used by reproductive endocrinologists for intrauterine insemination and in vitro fertilization are based on different cutoffs, such as total motile count. Our study also showed that 15.9%–19.3% of men would be reclassified as having normal morphology of >4% from having been abnormal in the past, i.e., <14%. The change in this parameter in determining the use of ART, especially intracytoplasmic sperm injection, is controversial and beyond the scope of the present discussion. Interestingly many reproductive endocrinologists already determine the need for ICSI based on 4% normal morphology and not 14% as originally suggested by Kruger and Coetzee (15). This is a paradigm shift that has come from practical application over time.

Another concern with the change in reference values is time to adopt them into the community even if they are validated. We previously showed that both ART labs and regional laboratories across the United States did not have a high compliance with the 1999 WHO semen analysis reference values 10 years after they were released. Overall, only 23% of laboratories (both ART and non-ART) reported reference values that complied with 1999 WHO semen analysis criteria (16). Interestingly, it was found that only 32% of ART labs were in compliance, mainly owing to nonadherence regarding morphology (16). This raises the question of how and when the fifth edition will begin to be used by specialists/laboratories and subsequently a change will be seen in who may or may not be referred to the appropriate andrologist for complete evaluation. We do not know the denominator for the number of semen analyses ordered nationally and then reviewed appropriately or inappropriately to determine referrals. The present study highlights this concern with the potential effect of the shift to the 2010 parameters, but it could not address the broader aspects of the problem. We suspect the problem is larger than we have reported, because even now many providers often do not refer men with parameters that are below previous reference values or recognize that there has been a change in reference values.

We recognize that there are several limitations to our study. We evaluated a large number of patients with only
one semen analysis. It has been known that fertility or sperm production can not be assessed on the basis of a single sample of semen (17). We decided to look at single semen analyses as a proof of principle. We did not want the single analyses to be excluded, because the objective was to see how many semen analyses would change from abnormal to normal. We thought that it was appropriate to consider each semen analysis on its own merits. We also wanted to look at another cohort with a realistic clinical scenario for evaluations with more than one semen analysis, i.e., the average of each parameter to correct for any natural variability. There was not a large difference in the changes for those with one analysis and those with the average of multiples analyses. Many times when referrals are made to infertility clinics, they are based on single analyses, and those may be individuals that would now have a “normal” analysis based on the new 2010 criteria and never get referred for a work-up for possible male factor infertility. Another relative limitation of our study is that we did not analyze the underlying diagnosis or outcome (if available) of the 15% of patients that would have changed from infertile to fertile. It would be interesting to expand on this issue to determine if those patients would have had any surgical or medical correctable reason or cause of the infertility. We did not have ART information if any was performed.

It is also important to remember that there are inherent limitations of the 2010 WHO study that defined the semen parameters for the new criteria. The study used only 4,500 fertile men spread out over fourteen countries with the reference values being the 5th percentile for the cohort (3). The need for large regional studies to define fertility may still be needed, and providers need to be educated on significance and limitations of reference values. However, whatever method and new reference range is used, the population with male factor infertility will shift if semen analysis remains the only mainstay of making the diagnosis. This may lead to potential underreporting as shown in the present study. Cooper et al., authors of the 2010 WHO study, specifically concluded that “the data represent sound reference distributions of semen characteristics of fertile men in a number of countries. They provide an appropriate tool in conjunction with clinical data to evaluate a patient’s semen quality and prospects for fertility” (3). The need to continue to have the male partner evaluated as part of the full clinical history/data of the couple is essential and the semen analysis remains a limited tool, not a substitute, for determining clinical care.

CONCLUSION

The change in semen analysis criteria may have some significant consequences, as stated in the present study. The clinical applications and predictive value of these changes will need to be determined. Change in the definition of male factor infertility along with reduced evaluation and investigation of the male partner is likely. Fewer men may be detected for treatable infertility and medical conditions, but it will probably take several years for the new criteria to be adopted and affect current decision making, especially for ART.

REFERENCES

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