Total Motile Sperm Count Trend Over Time: Evaluation of Semen Analyses From 119,972 Men From Subfertile Couples

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OBJECTIVE	To determine whether a clinically-relevant change in the total motile sperm count (TMSC) over time exists within the subfertile population.
METHODS	The first semen analysis of all men presenting to selected infertility centers in 2 countries between 2002 and 2017 were evaluated. Semen analyses were categorized into 3 clinically-relevant groups based on treatment options: TMSC >15 million (M) (Group 1), in which no insemination intervention would be required; TMSC 5-15 M (Group 2), in which intrauterine insemination would be appropriate; and TMSC of <5 M (Group 3), in which in vitro fertilization would be considered. Relationships between male age, TMSC, trend of TMSC, and TMSC group membership by year were assessed.
RESULTS	A total of 119,972 first semen analyses were included. The proportion of men with normal TMSC (>15 M) was found to decline approximately 10 percentage points over the past 16 years in the analysis of combined centers (odds ratio 0.967; 95% confidence interval = 0.963-0.971; P = 2.2e-16). A reciprocal increase was distributed between both the moderate (5-15 M) and severe (<5 M) oligozoospermia groups. Additionally, TMSC declined 1.1 percentage points with each year of advancing paternal age. No difference was seen in age at presentation by year.
CONCLUSION	The proportion of men with normozoospermia declined and that of men at risk of requiring fertility treatment increased over the study time period. Although several unknown factors may have influenced our data as a result of the retrospective design, a shift in treatment group membership over time may be clinically relevant. UROLOGY 132: 109−116, 2019. © 2019 Elsevier Inc.

Previous studies from centers worldwide show a downward trend in sperm counts over time in men unselected for infertility.[1-4] Findings from 2 prior meta-analyses, both publicized in the lay media, aroused concern from the general public.[5,6] Carlsen et al (1992) identified a significant decrease in sperm count from 113 million (M)/mL to 66 M/mL based on 61 papers from 1938 to 1991 including 14,947 men.[5] Levine H et al (2017) reported a 1.6% decline in mean sperm count (utilizing hemocytometers for measurement) per year after reviewing 185 studies from 1973 to 2011 of 42,935 men.[6]

These meta-analyses have limitations and, therefore, should be interpreted with caution.

Of primary concern is the considerable heterogeneity of the studies included in the prior meta-analyses. Specifically, the aforementioned studies included many studies over a duration of 53 and 32 years, respectively. Heterogeneity arising from various study designs, sperm counting methodologies, and geographic/ethnic differences are inevitable when such high numbers of investigators are involved and laboratory advancements occur over time. Additionally, translation of findings to the population seeking fertility treatment is challenging, as the meta-analyses excluded studies of infertile patients. Furthermore, a trend for sperm motility, and specifically, the total motile sperm count (TMSC), has not previously been reported. As compared with World Health Organization (WHO) 2010 parameters,[7] prewash TMSC has been found to have a higher correlation with both blastocyst development and expansion as well as ongoing pregnancy rate in both intrauterine insemination and in vitro fertilization cycles.[8,9]

While the heterogeneity between studies diminishes the conclusions that can be drawn from prior meta-analyses, these data, in addition to other mounting scientific evidence, leave little doubt that sperm counts are, in fact, declining over time.[1-6] What is less clear is the relevance of the decline. In order for a decline in sperm counts to be clinically relevant, sperm counts must drop below a threshold at which treatment is potentially required. Therefore, we sought to reframe the narrative on the sperm count trend over time by assessing the proportion of men within descending TMSC groups that were created based on recommended insemination treatment options. The null hypothesis was that changes in sperm counts over time have not altered the proportion of men at risk of requiring fertility treatment. Therefore, the study objective was to determine if the proportion of men within each total motile count categorization is changing over time, implicating a potential increased need for fertility treatment from a clinical perspective.

MATERIALS AND METHODS

Study Population
This was a retrospective study evaluating the first semen analysis (SA) of all men of couples presenting for infertility concerns at 2 large reproductive care systems, one in northeastern United States (Reproductive Medicine Associates of New Jersey, United States of America; denoted 'Center A') and the other in Spain (Instituto Valenciano de Infertilidad (IVI) Centers in Spain; denoted 'Center B') from 2002 to 2017 and 2011 to 2017, respectively. All included semen analyses were performed at one of the study reproductive care centers. Only records accessible electronically were included, which limited Center B's inclusion of semen analyses to begin in 2011. Both systems, rather than just one, were chosen for participation in this study in the attempt to improve external validity of the findings. All statistical analyses to answer study questions were performed separately on each center as well as on the combination of the 2. Figures of combined data are only included if the data from the 2 centers were aligned.

Males were referred for SA as part of a couple's evaluation for infertility. Males with retrograde ejaculation or history of vasectomy were excluded. Samples lacking record of collection date, male age, or TMSC were also excluded. Information regarding whether or not males were previously evaluated at another center was not available. The TMSC used for sample evaluation was obtained by multiplying the semen volume by the concentration and percentage of rapidly progressive and slowly progressive motility spermatozoa.

Semen Analysis
Male patients were instructed to maintain 2 to 7 days of sexual abstinence prior to sample collection. Semen analysis was performed according to the most current and accepted version of the *World Health Organization Manual for the Examination and Processing of Human Semen* at the time of patient presentation. External quality assurance and internal quality control were conducted in both systems throughout the duration of the study. As such, each center ensures that all new media, reagents, supplies and equipment are tested to ensure similar performance to established controls. Protocols are set in place for routine maintenance and calibration of all relevant equipment and are strictly adhered to. Additionally, each participates in a regional Proficiency Testing program, which all laboratory personnel must successfully complete prior to performing tests on clinical samples. Center A participates in the American Association of Bioanalysts Proficiency Testing Service, approved under the regulations of the Clinical Laboratory Improvement Amendments (CLIA'88). Proficiency evaluations take place monthly for 3 months and then quarterly. Parameters evaluated include sperm count, morphology, motility, and viability. If results of the proficiency testing are outside of the target ranges, remediation is performed until all technicians meet the accepted standards. Center B collaborates with other laboratories to carry out blind analyses on the same control samples. The consensual value obtained by all those who use the same method is used to make the appropriate comparisons and provide each laboratory with the knowledge of its similarity with the rest of the laboratories. Center B's National External Quality Control Programme for the semen analysis is conducted at the Centro de Estudio e Investigación de la Fertilidad (CEIFER) in Granada, Spain.

With respect to performance of the semen analysis, all criteria in the checklist detailed by Björndah L et al, 2016, were met by both centers with the exception of utilizing Makler counting chambers to count sperm.[10] This measurement should not impact the overall results, since any error (if existent) has been present for the entire study period.

Study Design
To determine if a change in sperm counts over time has clinical relevance, men were categorized based on TMSC. Three groups were created based on insemination strategy that would likely be recommended based on TMSC. Group 1 included men with TMSC greater than 15 million (M), and was considered to be the "no intervention" group, as a male patient with such a count would require no intervention for insemination.[8,11] Group 2 consisted of men with TMSC of 5 to 15 M, in which intrauterine insemination would be deemed appropriate. Finally, men with TMSC of less than 5 M (including azoospermia) comprised Group 3, for which in vitro fertilization with intracytoplasmic sperm injection would be considered.

Statistical Analyses
Descriptive statistics and visualizations were performed for Center A and B cohorts. Linear regression analysis was performed to test the associations between TMSC and the year of semen collection, and between TMSC and sperm age. Male age and collection year were controlled for as covariate terms in these analyses, respectively. For linear regression analyses, the TMSC was log10-transformed to approximate a normal distribution. Model assumptions of normally distributed residuals were checked and found to be satisfying. Logistic regression was used to test the relationship between odds of membership in Groups 2 and 3 (TMSC <15 M) vs. Group 1 (TMSC >15 M) by sperm collection year with sperm age as a covariate. Grouped and independent analyses were performed on the Center A and B data as appropriate.

Ethical Approval
Patients were consented for the use of deidentified information utilized for retrospective scientific inquiry. Institution Review Board (IRB) approval was granted for retrospective database queries in January, 2016 for the Center A site (RMA-2015-03). Approval was granted for the Center B site by the Institutional Review Board from IVI Valencia in March, 2018 (1802-FIVI-017-NG).

RESULTS

Study Participants

A total of 161,555 first SAs were identified: 45,111 SAs from unique Center A patients and 116,444 from unique Center B patients. Of note, 129 countries of origin were described in the Center B cohort, although the majority of patients reported Spanish residence (74.9%). Country of residence was not available for Center A. After application of exclusion criteria, a total of 119,972 first semen analyses remained: 41,809 SAs from Center A and 78,163 SAs from Center B. Data was available and accessible via electronic medical record from 2002 to 2017 from Center A and from 2011 to 2017 from Center B (Supplementary Figure 1). No changes in referrals to the centers during the study duration were known.

Overall TMSC Frequencies Over the Study Period

The frequency of all TMSCs obtained from semen analyses from each center over the study period are depicted in the frequency plots in Supplementary Figures 2a and b. These figures depict the frequencies of all TMSC identified from semen analyses from Clinics A and B. The majority of semen analyses revealed TMSCs >15 M as demonstrated by the graphs. The distribution of semen analyses follows a more continuous pattern for Clinic B than Clinic A, but for both clinics, a second peak in frequency is noted when TMSC is <1 M.

TMSC Trends by Year

The overall median total motile counts of the Center A and Center B populations were 74.4 M and 60.3 M, respectively. The median and interquartile ranges of TMSCs of each clinic by year are represented in Figure 1. When evaluating the TMSC trends over time, Groups 1 (TMSC >15 M) and 3 (TMSC <5 M) of both clinics were evaluated separately. The reason for this was that the vastly different TMSCs in these groups is thought represent a difference in underlying biology, and therefore, a trend in one group may not accurately reflect the trend of the other. Figure 2a demonstrates a very slight decline in TMSC over time within the normal, or "no intervention" group (TMSC >15 M) ($P = 2e{-}16$), while an increase in the proportion of semen analyses with TMSC <5 M was seen (Fig. 2b) ($P < 2.2e{-}16$). However, these results alone do not offer information with respect to fertility treatment implications, so we sought to specifically evaluate the *proportion* of men within each treatment category (Groups 1, 2, and 3) over time.

### Proportion of Men Within Each TMSC Group Over Time

The proportion of men with normal TMSC (>15 M) presenting for care was found to decline slightly over time for each center (Center A: odds ratio [OR] 0.982; $P = 2.2e{-}16$; Center B: OR 0.979; $P = 2.8e{-}16$). A combined analysis of both centers revealed a decline of approximately 10 percentage points over
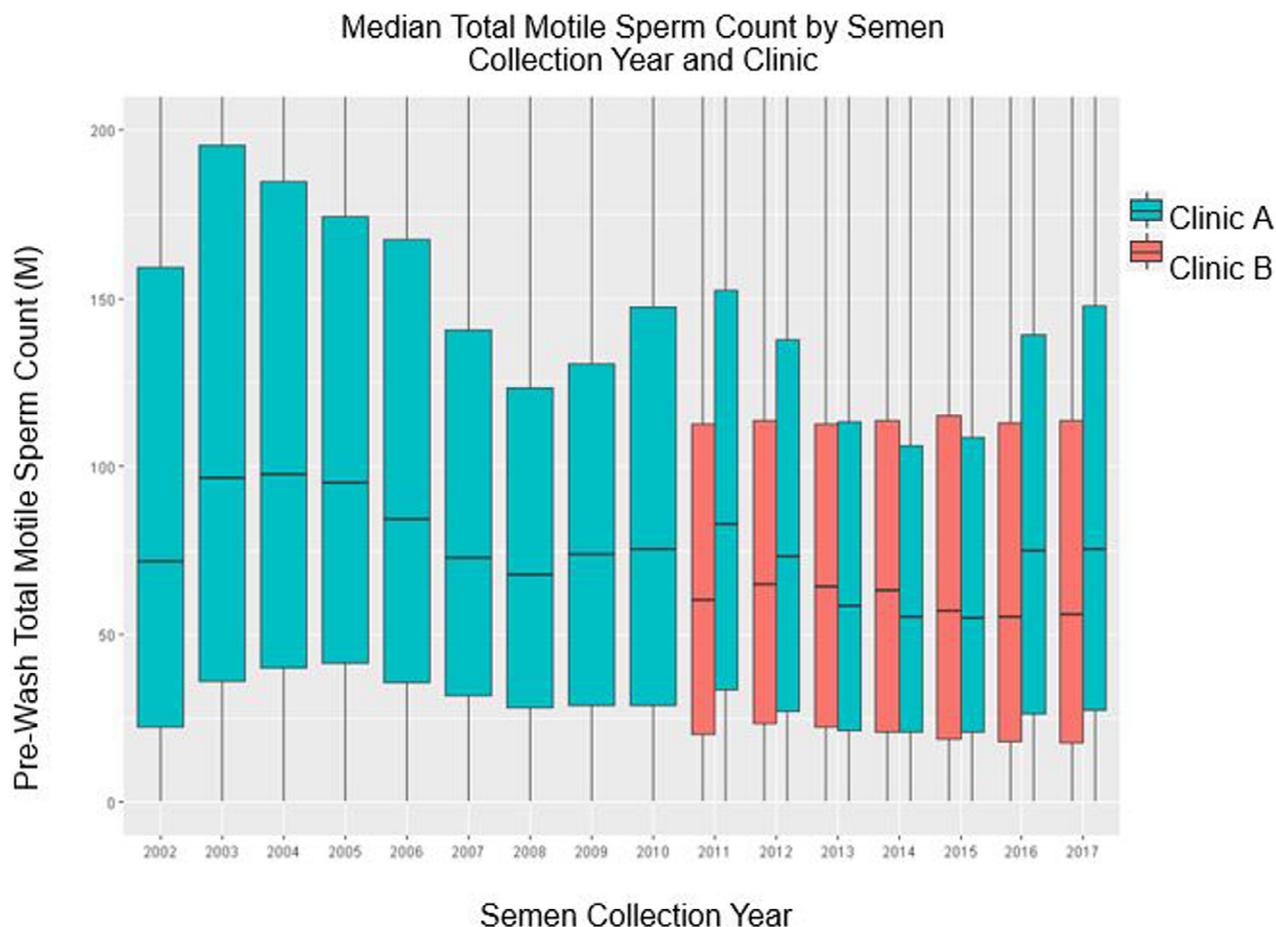
Figure 1. The overall median total motile counts of the Center A and Center B populations were 74.4 M and 60.3 M, respectively. The median and first and third quartiles of TMSCs of each clinic by year are represented in the box plot below. TMSCs, total motile sperm counts. (Color version available online.)
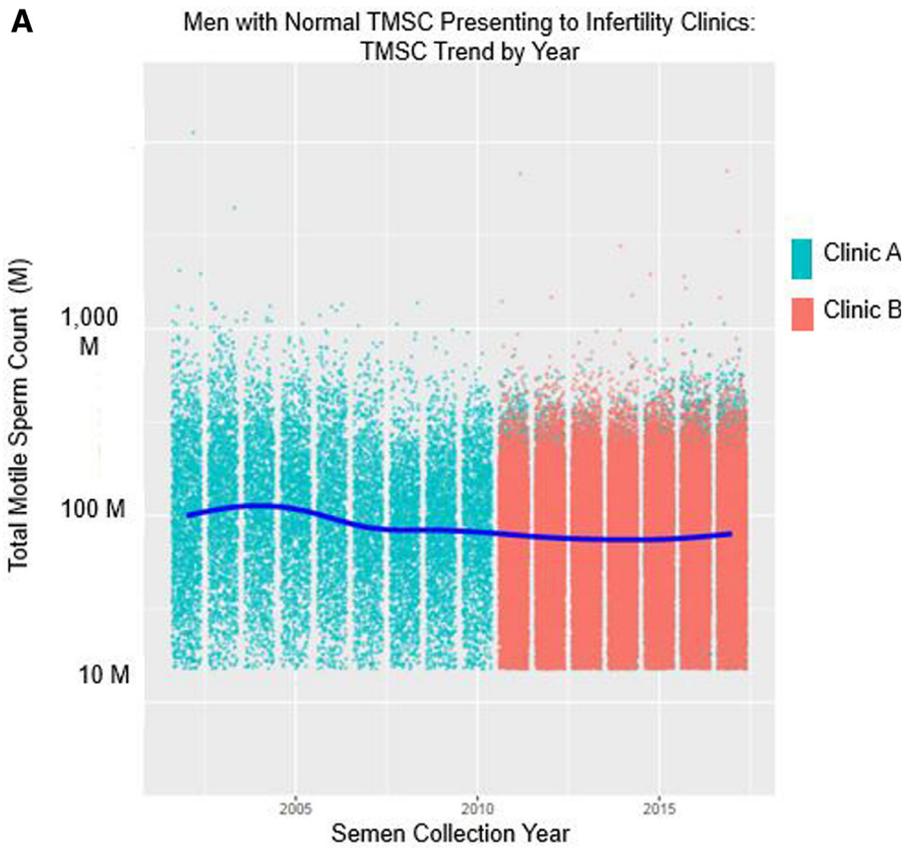
Figure 2. (a) Density plot of combined clinic data demonstrating the TMSC trend over the study period of men with normal TMSC (>15 M) presenting to infertility Clinic A (United States) and B (Spain). A slight decline over time was identified ($P = 2e\text{-}16$). (b) The proportion of men presenting for evaluation from both clinics with severe oligozoospermia or azoospermia increased over the study duration ($P <2.2e\text{-}16$). Error bars represent standard error. (Color version available online.)

Proportion of Men Presenting to Two Infertility Centers
In Each TMSC Group by Year
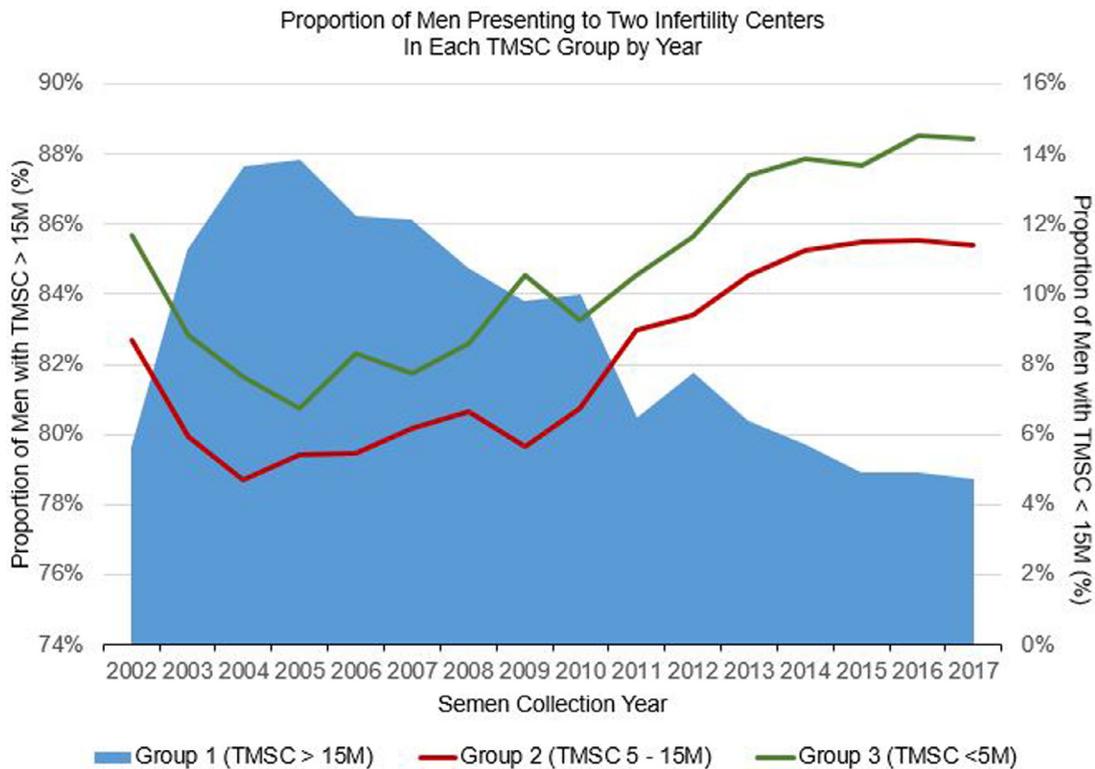
Figure 3. The proportion of men with normal TMSC (>15 M) was found to decline over the past 16 years (OR 0.967, 95% CI = 0.963-0.971; P = 2.2e-16). A complimentary increase in the proportion of men with TMSC of 5 to 15 M and TMSC <5 M was also seen. CI, confidence interval; OR, odds ratio. (Color version available online.)

the past 16 years (P = 2.2e-16). Reciprocal increases were seen in not only the moderate oligozoospermia group, but also in the severe oligozoospermia/azoospermia group (Fig. 3). Therefore, the proportion of men presenting with TMSCs not requiring intervention declined to an extent significant enough to alter group membership over time.

TMSC and Male Age
Total motile sperm count was found to significantly decline with increasing male age, as has been previously described for other semen parameters (Fig. 4). For every 1-year increase in age, the TMSC declined 1.1% per year (P = 2.2e-16). We postulated that perhaps older men presenting each year might explain our findings; however, this was not the case, as the age of men delivering semen samples each year remained consistent over time for both centers (median age 36.2 years).

DISCUSSION
This is the largest evaluation of semen analyses (n = 119,972) and the only known analysis of total motile count trend in the subfertile population. Secondly, clinical relevance of such a decline was demonstrated through the evaluation of membership within treatment-related TMSC categories over time. As group membership is synonymous with diagnostic category, a change in categories implies a potential need to alter clinical management. Our findings indicate that the proportion of men at risk of requiring fertility treatment has increased over time.

Specifically, the proportion of men with normozoospermia was found to decline by 9 percentage points (87.6% to 78.7%) over the past 1.5 decades in this sample of men from subfertile couples presenting to 2 large infertility centers. The downward trend is associated with a reciprocal increase in the proportion of men at risk of requiring fertility treatment: In 2017, the percentage of men with abnormal TMSC presenting to our infertility clinics was 21.3%, up from a nadir of 12.4% in 2004. Additionally, our findings of reduced semen quality with increasing male age corroborate those of other investigators. Notably, TMSC was estimated to decline 1.1% with each year of advancing male age. If our findings are substantiated in the fertile population, a stronger impact may be seen, as a prior analysis of 168 million births from 1972 to 2015 identified an increase in the average age of paternity in the general population.[12] However, the average male age in our population of subfertile men actually remained constant over the study time period of 16 years.

An additional strength of this study includes the inclusion of only 2 centers. Within these 2 organizations, interobserver variability in sperm counting methodology and ascertainment bias is minimized through standardized andrology technician training and application of internal and external quality controls. However, the most significant strength of this study is the large sample size. Previously, the largest study on sperm count trend included 42,935 men, which is one-third of the number analyzed in

Total Motile Sperm Count of Men Presenting to Infertility Clinics A and B by Increasing Male Age
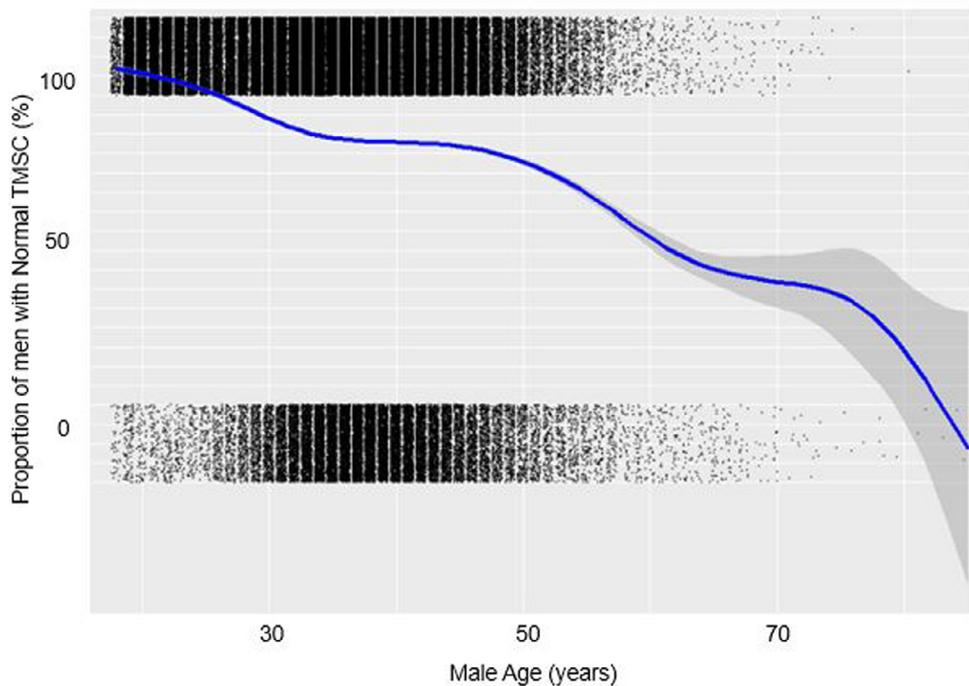
Figure 4. A density plot in which each black dot represents a semen analysis with TMSC of the specified value. Therefore, darker areas correspond with higher density of TMSC values. The top bar represents men whose TMSCs were >15 M and the bottom bar represents men with TMSCs <15 M. A logistic regression is fit through the data points, demonstrating that the proportion of men presenting to Clinics A and B with a normal total motile sperm count significantly declined with increasing male age (OR 0.977, 95% CI = 0.973-0.981; P = 2.2e-16). (Color version available online.)

the present study. A final strength of this study is the inclusion of 2 geographic regions: northeastern North America and Spain. The sample from Center B was comprised primarily of men of Spanish origin (74.9%), however, the remaining proportion (25.1%) reported 128 different countries of origin, somewhat enhancing the external validity of study findings.

Limitations of the study derive from its retrospective design. For example, the inclusion of 2 centers may be regarded as a limitation as well as strength. It might be speculated that noteworthy differences exist between countries with respect to cultural philosophy on infertility treatment and/or management, insurance reimbursement, and/ or criteria for referral to an infertility clinic. Additionally, several other unknown factors may have influenced our data, such as a change in the population of men referred for care throughout the study time period. Specifically, there may have been an increase in couples with more severe male factor infertility presenting to these centers over time, possibly as a result of increasingly strict criteria for referral as assisted reproductive technologies evolve. However, there is no evidence that this was the case. Furthermore, the dataset was limited to semen analyses available in the electronic medical record, with more data lost from Center B (ie, prior to 2011) as a result of missing information. Finally, many factors with the potential to affect sperm count or motility over time were not

evaluated, as this information was not available. Such factors include past medical and surgical histories,[13] occupational exposures,[14] medications,[15-17] body mass index or presence of obesity,[18] dietary and exercise habits,[19] tobacco use,[20] and/or substance abuse history.[21] However, even when such factors are known, concern still exists regarding the imprecise methods through which such risk factors are identified. Arguably, the decline is still a matter of concern regardless of cause.

Regional differences in the distribution of TMSCs were identified (Figs. 2a and b), however, influencing factors were not examined in this study. Such dissimilarities possibly reflect differences in biology but more likely reflect differing referral patterns between Center A and B. Previous studies have identified geographic variations in standard semen parameters, however, further study is needed to determine if such differences in TMSC truly exist[22] in both the subfertile population as well as one unselected for infertility. Although conclusions are limited due to those inherent of a retrospective design, if the trends identified reflect true processes in nature, perhaps environmental and lifestyle influences play a significant role.

Many excellent contributions have been made toward investigating potential underlying causes of the trend of reduced semen quality. Available evidence suggests that various genetic factors (eg, polymorphisms and defects),[23] exposures in-utero[24] and postnatally[25] to endocrine

disrupting chemicals, particularly phthalates, bisphenol A,[26] polychlorinated biphenyls, pesticides and organophosphates,[27] and toxic lifestyle behaviors[28,29] may adversely affect sperm count and/or motility. However, the impact of these factors, both individually as well as in conjunction with other influences, is largely unknown. Assessments of the relationship between environmental and lifestyle factors and sperm quality are significantly limited by the inability to account for all possible confounding exposures. For example, potentially impactful in-utero exposures may not be known when a patient presents for infertility work-up and management approximately 25 to 50 years later. Therefore, studies aimed at identifying the underlying etiologies of a decline in sperm counts, especially with a prospective design, are very difficult to conduct. Such study design barriers somewhat limit our understanding in this area, but nonetheless, uncovering the complex interplay of etiologies affecting sperm counts is an important matter to pursue.

Analysis of the shift in diagnostic categories over time confers clinical relevance to the sperm count trend with respect to infertility management. However, on a macroscopic level, such a trend heralds an even greater concern with regard to overall male wellbeing. Reduced sperm count has been identified as a biomarker of male health, as several studies have shown that abnormal semen parameters are associated with morbidity and mortality, and may also impact the health of offspring.[30] Such associations highlight this field of study as an important avenue to investigate from the public health perspective.

As discussed, evaluation of sperm count trends over time is difficult given the numerous confounding factors. However, mounting evidence suggests that sperm counts are, in fact, declining over time, which is also associated with a shift in diagnostic categories as evidenced by these data. Such shifts (ie, normozoospermia to oligozoospermia) likely result in altered management of infertility. Future directions may include the determination of intrapatient variability of TMSC over time and the development of a validated TMSC classification system. Additionally, an analysis of longitudinal trends by infertility diagnosis would be of interest, as well as repeat meta-analysis of sperm count trends including studies of infertile patients. Finally, continued investigations of factors suspected to influence TMSC, along with proposed interventions, are urgently needed.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.06.038.

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EDITORIAL COMMENT

Sperm counts have been declining over the past 50 years, and this issue has recently generated increased concern within the general population after a study by Levine et al demonstrated a >50% decline in sperm counts, particularly in Western countries, from 1973 to 2011.[1] While it has been clearly shown that sperm counts are decreasing with time, the clinical significance of this is less clear. Total motile sperm count (TMSC) is an important semen parameter commonly used by fertility providers to determine a couple's candidacy for various assisted reproductive technologies (ART), and has previously been shown to be a better predictor of pregnancy outcomes than WHO classification values.[2]

Here the authors aimed to evaluate trends in TMSC over time for couples presenting with subfertility. They demonstrated a decrease in the proportion of men presenting with normal TMSC, and an increase in the proportion of men with low TMSC presenting for subfertility over time. While this data raise interesting questions regarding changes in clinically relevant semen parameters, it is difficult to determine whether these trends reflect an actual change in the general population, or simply a change in selectivity of patients being referred for abnormal semen parameters.

While the authors suggest that an increase in the proportion of men with low TMSC would reflect possible changes in the type of ART required, it would be important to determine if these increases translate to actual changes in ART practices. Studies have shown that the use of ART including intrauterine insemination and in vitro fertilization have increased over time, along with the proportion of people worldwide conceived by ART.[3,4] Does this reflect a growing need for ART, or an improvement in access to ART services? The authors present a thought-provoking study with a large sample size, which supports the alarming trend of decreases in semen parameters over the years, and should further prompt our field to investigate reversible reasons for these declines before it's too late.

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AUTHOR REPLY

The authors would like to thank Krzastek and Smith for the concise summary of our findings and discussion in their editorial comment.

As highlighted by Krzastek and Smith, a major limitation of this study was its retrospective design, resulting in the inability to determine if changes in clinically relevant semen parameters over time reflect a change in biology or referral patterns. Although there is no evidence to believe that the latter is the case, a prospective study is better suited to evaluate such a confounder. Additionally, future prospective studies on sperm counts in infertile and subfertile populations should investigate whether the increased utilization of assisted reproductive technologies (ART) is secondary to enhanced access to care vs a higher need for ART. As an active issue, it is unclear how access to ART has changed clinical practices in any given location. Such a future study might simultaneously evaluate the frequency of use of various ART and patients' infertility treatment insurance coverage or lack thereof. Information from clinicians regarding the degree to which management decisions are based on financial considerations may also be required.

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