Accepted Manuscript

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Please cite this article as: Yash S. Khandwala, Chiyuan A. Zhang, Shufeng Li, Barry Behr, David Guo, Michael L. Eisenberg, Racial Variation in Semen Quality at Fertility Evaluation, *Urology* (2017), http://dx.doi.org/doi: 10.1016/j.urology.2017.03.064.

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Racial Variation in Semen Quality at Fertility Evaluation

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Abstract

Objective: To identify racial differences in semen quality among men living in the same geographic area seeking fertility evaluation.

Methods: Men obtaining a semen analysis for infertility evaluation or treatment between 2012 and 2016 at a single center were identified and demographic data including height, weight, BMI and age were described. Mean semen parameters and the proportions of men with suboptimal parameters based on the WHO 5th edition criteria were also compared based on race. Multivariable regression analysis was conducted incorporating age, BMI and year of evaluation. Further sub-analyses based on BMI were subsequently performed.

Results: White men produced greater volumes of semen on average, however, Asian men had higher sperm concentrations and total sperm count. A lower proportion of Asian men compared to White men had semen quality in the suboptimal range for most semen parameters while a higher proportion of white men were found to have azoospermia. Stratification by BMI groups attenuated the observed differences between Whites and Asians, yet Asian male semen quality remained higher.

Conclusions: Among men evaluated for infertility at a single center, Asians had lower volume but higher sperm concentrations compared to Whites which was influenced by differences in azoospermia prevalence. While anthropometric and demographic factors attenuated the differences, even after adjustment, the contrasts remained. Our study suggests racial differences exist in semen quality at the time of infertility evaluation.

Keywords: Racial Disparity, Male Infertility, Semen Quality

Introduction

Natural variation in the semen parameters between fertile men makes it difficult to establish universal reference values for semen quality. Having an accurate characterization of what constitutes normal semen is unquestionably valuable as it can help guide the diagnosis and management of infertility.[1]

The World Health Organization reviewed the world's literature and defined normal semen parameters through the publication of laboratory manuals, however, there is much debate regarding the global applicability of these definitions.[2,3] For example, most of the subjects involved in the WHO manual come from countries in the northern hemisphere (with the rest originating in Australia) and fertile men from China, India, Africa and South America are notably underrepresented in the study cohort (with only one out of eight studies representing populations outside of North America or Europe).[3,4]

Several recent findings and a comprehensive review have commented on the impact of race and geography on semen analysis results.[3,5–10] Black men were found to have lower mean semen volume, sperm concentration, total sperm count and total motile sperm than white or Hispanics.[5,11] Moreover, men from semi-rural and agricultural regions produced lower sperm concentration and motility than their urban counterparts resulting in disparities in semen parameters throughout the continental United States.[5,6] These findings of racial and geographic variations in semen parameters were corroborated independently by investigators in Canada, Europe and Asia with some even suggesting the need for race-based reference values.[7,8,12,13]

Unfortunately, prior studies evaluating Asian and Caucasian semen parameters acquired semen analyses by pooling each racial group from different locations thus introducing geographic confounding.[4–6,9,10] This made it difficult to both isolate a man's race from

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environmental and lifestyle influences, and subsequently develop reference values specific to race. Despite the significant need for understanding normative semen values and the important role that race and ethnicity play in the establishment of these parameters, there appears to be a gap in the literature defining a standard that may be applicable to more than one demographic. Thus, this retrospective study aims to directly compare the semen quality of White and Asian men seeking infertility care within the same geographic area to further understand semen parameters for two populous races within a single multi-ethnic society.

Methods

Subjects

Subjects in our study were selected from the Stanford Translational Research Integrated Database Environment (STRIDE) research and development project that contains a database of over 2 million pediatric and adult patients since 1994. The cohort included men obtaining a semen analysis between January 2012 and August 2016 from a single Reproductive Endocrinology and Infertility lab utilizing computer assisted semen analysis (CASA). Semen samples acquired from these men were analyzed for parameters such as volume, concentration, total sperm count, sperm motility, sperm morphology, and prior days of abstinence. For men with multiple semen analyses, only the first test was included in the current analysis. However, all analyses were repeated using all available semen analyses for patients with no differences in conclusions noted. The semen parameters were analyzed as continuous and dichotomous based on WHO 5th edition criteria.[2] Sperm morphology, however, was analyzed based on the Kruger

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scale (with a normal morphology cut-off of 14%), consistent with the practice of our laboratory at the time of this study. Men with a history of vasectomy were excluded.

Demographic and anthropometric data was obtained via the electronic medical record. Men were identified as White or Asian based on how they self-identified in health care surveys and subsequently were ascribed in the STRIDE database. Our analysis focused on White and Asian men because they were the two most common races in our cohort as well as the most reliably classified.

Statistical Methods

Demographic, anthropometric data and semen parameters were described as means +/- standard deviation. Categorical variables were presented as counts with percentages. Wilcoxon rank-sum tests were used to compare semen parameter values and days of abstinence between Whites and Asians. The distribution of semen parameters was evaluated for normality with the Kolmogorov-Smirnov univariate normality test. Variables that were not normally distributed were square-root or cube-root transformed. Linear regression was applied to compare White and Asians over semen parameter values adjusting for age, BMI, year of evaluation and days of abstinence.

Chi-square analysis was performed to compare the percentage of abnormal semen parameters between the two races before and after BMI stratification as obesity has been shown to be significantly associated with an increased prevalence of azoospermia and oligozoospermia.[14] Multivariable logistic regression models incorporating age and year of evaluation were also conducted after stratifying for BMI to predict the likelihood of each race having abnormal semen parameters as defined by the WHO laboratory.[2] Odds ratios are

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presented with their 95% confidence intervals. All statistical tests were two-sided with the

significance level set at P <0.05. All analyses were performed using SAS 9.4 (Cary, NC).

Results

Our cohort consisted of 1,230 (64%) White men and 701 (36%) Asian men. White men

in the cohort were older, taller and heavier than the rest of the population. There were also a

notably higher percentage of obese white men (9.4%) compared to Asian men (5.6%)

(P=0.0007). Table 1 details the baseline characteristics of the two cohorts.

Whites had higher semen volumes than Asians (2.9 mL vs. 2.6 mL; p = 0.001), while

Asian males had higher sperm concentrations (60.9 million/mL vs. 51.3 million/mL; p <0.0001,

Table 2). Asians tended to have a higher average total sperm count compared to White males, but

a lower total motile sperm count. The percentages of morphologically normal spermatozoa and

motile spermatozoa were similar between White and Asian men. Overall, White men had fewer

mean days of abstinence (3.7 days) than Asian men (4.2 days) prior to semen analysis (p=0.002),

but a difference in 0.5 days is likely not clinically significant. The patterns in semen quality

remained in the fully adjusted models (adjusting for age, BMI, year, and days of abstinence).

Using the WHO parameters as a reference standard, no significant difference was found

between the proportions of White and Asian men with suboptimal semen volumes of less than

1.5 mL. When considering the proportion of each race with oligospermia (sperm concentration

<15 million/ mL), only 16.4% of the Asian male semen samples were suboptimal compared to

29.3% for White men (p < 0.0001). The proportions of Asian men with a low total sperm count

(< 39 million), low percentage of motile sperm (<40%), and low total motile sperm count (<9

million) were also significantly lower than for White men. There was no significant racial difference in proportions of men with low percentage of morphologically normal sperm (<14%). Results are further enumerated in Table 3.

Of the 1,931 men in our cohort, 323 were azoospermic (16.7%). White men had the highest proportion of azoospermia with 20.7% compared to 9.9% of Asian men (p < 0.0001). When subjects were categorized by number of semen abnormalities (volume, concentration, motility and/or morphology), 579 of all participants (30.0%) were found to have normal semen with a higher proportion of Asian men, 35.1% (246 men), having no abnormalities compared to White men, 27.1% (333 men). A fewer percentage of Asian men also had one, two, or three semen abnormalities compared to their counterparts which likely contributed to the overall disparity in semen quality noted between the two races.

A separate comparison of semen parameters was conducted after excluding all men without motile sperm. White men still had higher semen volumes (3.0 mL vs. 2.7 mL; p =0.0004) while Asians continued to have higher sperm concentrations (67.5 million/mL vs. 64.6 million/mL; p =0.036). However, significant differences in total motile sperm and total sperm between races were no longer identified.

Given the differences in BMI between Asian and White men in the cohort and its known influence on semen quality, semen parameters were recalculated after stratifying by BMI groups (normal weight, overweight, and obese; Table 4).[14] The same general trends were seen across BMI categories as were observed for the whole cohort. Even after adjusting for patient characteristics, Whites had 1.87 times the odds of having a semen analysis with suboptimal sperm concentration compared to Asians (p < 0.0001).

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Overall, Asian men tended to have fewer total number of semen abnormalities than White men and were also less likely to be azoospermic. The one exemption to this trend was in the obese BMI group.

Discussion

Variation in semen parameters among races within the same local geography has not previously been identified. Using a large database of men seeking infertility evaluation, we were able to compare semen parameters between men who identified as White or Asian. White men had higher semen volume on average than Asian men but their mean sperm concentration, total sperm count, percent of motile sperm and percent of morphologically normal sperm were significantly lower. A larger proportion of White men compared to Asian men had suboptimal sperm concentration, total sperm count, percent motile sperm and total motile sperm count. Asian men also tended to have fewer semen abnormalities and a smaller proportion presented with azoospermia compared to White men.

In general, White men produced a higher volume but with a lower sperm concentration than Asian men, even after the exclusion of all patients with azoospermia. This racial difference in semen parameters seems to be attenuated by body mass index. Indeed, Whites on average were larger compared to Asians, however, across most BMI strata White men consistently had lower semen parameters. While days of abstinence was significantly different between the two groups, it did not affect our conclusions after incorporation into the regression model.

Other groups have compared semen quality between races. Gao et al. examined semen quality of Chinese men and found that semen parameters were lower than the WHO standard, which was developed using primarily White subjects. Sperm motility and viability were

especially inferior to the published reference values.[8] Another study by Iwamoto et al. in 2006 included 324 fertile Japanese men and discovered that the semen quality, except for sperm motility, of Japanese men are equivalent to that of Danish men, who purportedly have the lowest among men in Europe.[9] However, semen in this study was acquired from various centers across Asia and Europe. Thus, the authors suggested that lifestyle or environment could be responsible for variable semen quality as geography has been shown to significantly influence semen quality in Europe, Asia and the United States.[6,9,10,13] Also, different laboratories have unique collection and analysis methods significantly influencing the results.[4] Notably, our study included only the first semen analysis ascribed to each patient. This methodology has been validated previously, as little difference was been noted between multiple semen analyses acquired for fertility testing within a short period of time, especially when evaluated by the same laboratory.[5] Nevertheless, we completed all analyses using all available semen data and found no difference in our conclusions.

Literature published by the Study for Future Families (SFF) found that semen quality varied across regions of the United States. As lower semen parameters were identified in rural areas, the authors hypothesized environmental exposures (e.g. pesticides) may explain the geographic differences.[5] Thus, when studying racial differences in semen quality, examining a single geographic region may help minimize confounding factors such as laboratory or environmental variation. Comparing races from different regions of the country or world may complicate the interpretation. The SFF adjusted for location by comparing total sperm count of Blacks vs. Whites within each testing center and found that Black subjects had fewer total sperm than Whites. However, the study did not include Asians, possibly due to an insufficient population size, and only tested a single semen parameter—total sperm count.[5]

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While Asian men in our study were found to have higher quality semen than White men, several differences were apparent in other characteristics as well. Specifically, Whites were older, heavier, and had shorter abstinence intervals compared to Asians – all of which may impact semen quality.[15–17] Yet even after adjustment for these factors, Asian males displayed higher sperm concentrations, total sperm count and total motile sperm count and were less likely to present with abnormal semen quality compared to Whites. While biological differences in sperm production are possible, other etiologies likely exist such as differences in cultural tendencies. For example, Asian men may seek infertility evaluation after fewer months of attempting to conceive; thus, the men who present for care may be not meet the definition of infertility and, in fact, have normal sperm quality. Indeed, data does support a difference in seeking a male evaluation based on race.[18]

Overall, 16.7% of our infertile cohort were azoospermic which is similar to prior literature suggesting that 10 to 15% of all infertile men produce semen devoid of viable sperm.[19] Certain obstructive conditions such as mutations in the CFTR gene are more common in Caucasian populations which may explain these discrepancies.[20] However, differences in infertility care seeking between Whites and Asians may also explain the difference in rates of azoospermia between the races.

Another possible explanation for the difference in semen quality between races is that Asian couples may be more likely to attempt conception at younger ages compared to White couples, a theory supported by our data.[21] A recent study by Martinez et al. based on 2006-2010 data from the National Survey of Family Growth (NSFG) examined the probability of first birth by selected ages for men of various races. While the probability of having a first birth before the age of 40 was higher for Asian men than White men (80% vs. 71%), White men had a higher

probability of having a first birth before the age of 30 (47% vs. 29%). Our cohort similarly contained a higher percentage of White men seeking infertility under the age of 30 and also a higher percentage seeking infertility after the age of 40 compared to asians.[22]

Additionally, Asian men have a lower BMI on average than White men as there is a smaller proportion of obese Asian men in our cohort.[23] Several studies using data from the National Health and Nutrition Examination Survey (NHANES) suggest that Asian children and adults tend to have a lower BMI than Whites. Another study by Wang et al. found that mean BMI of White men (25.1) was significantly greater than that of Asian men (23.4).[23–25] Although White obese men have higher quality semen than their Asian counterparts, a discrepancy in the number of subjects between the two groups could help explain the racial disparity found in our results. Men with higher BMI have lower semen quality and white men in our cohort tended to have higher BMIs than Asian men.[14,16] It is likely, however, that a combination of these extraneous factors along with genetic and biological influences explain the true difference in semen quality displayed between White and Asian men.

Furthermore, the development of stringent yet applicable reference values for semen parameters is crucial to the maintenance of men's health. The current WHO manual, unfortunately, only represents a portion of the global population (with only one out of eight studies representing populations outside of North America or Europe) yet its reference values are being used globally to predict fertility, evaluate fitness and guide treatment.[3,26–30] There is already substantial evidence supporting the variation in semen quality among diverse locations and there is growing sentiment that natural variation in semen parameters among various races exist.[3,5–7,12,13] A longitudinal evaluation to determine fertility success based on this variation is required before specific changes to the WHO criteria can be suggested. Although race-based

standards for optimal semen parameters is not a fully personalized model, understanding the effects of race and genetics on semen quality has great utility.

Certain limitations exist for our study. The retrospective design makes it difficult to further categorize race into specific ethnicities. The terms White and Asian are vague and non-descriptive. Yet, the purpose of this study was primarily to illustrate the racial differences in quality of semen rather than to comprehensively characterize it, and the lack of specificity does not detract from the significance of our findings. Future studies should include other races and ethnicities (e.g. African Americans, Hispanics, etc.). In addition, other relevant health and lifestyle factors were not available and should be incorporated in future studies (e.g. smoking, drinking, presence of varicocele, testicular size, etc.). While most of the men seeking care at our institution are from the same geographic region (90% of patients reside within a 50 mile radius), there is a distinct possibility that some patients travel long distances to be seen at our clinics which may contribute to some geographic variation. Also, our study population consists of men seeking infertility evaluation while previously cited reports included only fertile men. While the generalizability of the findings to fertile men remains uncertain, the characterization of differences in semen parameters among men seeking care is equally valuable as this population is the most likely to benefit from future studies.

Nevertheless, the discovery of a significant differences between the semen quality of Asian and White men seeking infertility care living in the same geographical area may have clinical ramifications. Further investigation is required to clarify the association of race with semen quality and to determine if more representative reference standards are needed.

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Table 1. Demographics.

		White	Asian	p
N (men)		1230	701	
Height (cm), avg (sd)		180.0 (7.6)	174.4 (7.5)	<.0001
Weight (kg), avg (sd)		87.3 (18.4)	78.8 (15.8)	<.0001
BMI (kg/m2), avg (sd)	Mean	26.6 (4.9)	25.6 (4.3)	0.0007
	Normal	267 (21.7)	170 (24.3)	
	Overweight	307 (25.0)	142 (20.3)	0.0007
	Obese	115 (9.4)	39 (5.6)	
	Missing	541 (44.0)	350 (49.9)	
Age (years), avg (sd)	Mean	39.7 (10.2)	37.8 (7.7)	<.0001
	<30	136 (11.1)	67 (9.6)	
	30-39	612 (49.8)	426 (60.8)	<.0001
	40-49	331 (26.9)	171 (24.4)	
	50+	151 (12.3)	37 (5.3)	
Year of evaluation	2012	317 (25.8)	227 (32.4)	
	2013	276 (22.4)	148 (21.1)	
	2014	215 (17.5)	122 (17.4)	0.0192
	2015	284 (23.1)	130 (18.5)	
	2016	138 (11.2)	74 (10.6)	

Table 2. Mean Semen Parameters.

Mean (SD)	White	Asian	p	Multivariate Model p
Semen volume (mL)	2.9 (1.6)	2.6 (1.4)	0.0011	<0001
Sperm concentration (million/mL)	51.3 (50.4)	60.9 (47.2)	<.0001	<0.001
Total sperm count (million)	146.2 (173.1)	157.0 (148.2)	<.0001	0.002
Percentage of motile spermatozoa (%)	39.0 (24.0)	40.6 (22.7)	0.1399	0.192
Percentage of morphologically normal spermatozoa (%)	15.7 (9.4)	16.1 (9.0)	0.3207	0.078
Total motile sperm count	80.8 (124.7)	80.5 (95.6)	0.0004	0.017

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Table 3. Number of men with Suboptimal Semen Parameters. N (%).

	White	Asian	p
Semen volume (<1.5 mL)	184 (15.0)	112 (16.0)	0.567
Sperm concentration (million/mL) <15M/mL	360 (29.3)	115 (16.4)	<0.001
Total sperm count (million) (<39M)	395 (32.1)	142 (20.3)	<0.001
Percentage of motile spermatozoa (<40%)	618 (51.4)	320 (46.2)	0.030
Percentage of morphologically normal spermatozoa (< 14%)	450 (45.3)	225 (41.7)	0.184
Total motile sperm count (<9M)	389 (31.7)	163 (23.3)	<0.001

Table 4. Number of men with Suboptimal Semen Parameters by BMI. N (%).

	White			Asian				
	Normal Weight	Overweight	Obese	Normal Weight	Overweight	Obese	OR (95%CI)	p
Semen volume (<1.5 mL)	42 (24.7)	22 (15.5)	11 (28.2)	43 (16.2)	53 (17.4)	26 (23)	0.70 (0.53–0.94)	0.016
Sperm concentration (<15M/mL)	36 (21.2)	37 (26.1)	11 (28.2)	86 (32.2)	101 (32.9)	38 (33)	1.87 (1.44 - 2.42)	<.001
Total sperm count (<39M)	48 (28.2)	43 (30.3)	15 (38.5)	94 (35.2)	112 (36.6)	46 (40)	1.57 (1.23 - 2.00)	<.001
% motile spermatozoa (<40%)	95 (56.6)	68 (48.9)	23 (60.5)	145 (56)	162 (54.7)	70 (62.5)	1.19 (0.98 - 1.46)	0.082
% morphologically normal spermatozoa (<14%)	70 (48)	45 (37.8)	20 (52.6)	109 (48.4)	126 (48.1)	51 (49.5)	1.17 (0.94 - 1.47)	0.162
Total motile sperm count (<9M)	56 (32.9)	41 (28.9)	15 (38.5)	96 (36.1)	110 (36)	43 (37.4)	1.32 (1.05 - 1.67)	0.016

Genetic biomarkers underscore the difficulties in elucidating racial differences in semen analyses.

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Short title: Differences in semen analysis associated with race.

Key words: Genetics; race; semen analysis; biomarker; glutathione transferase; antioxidant;

CAG repeats

Word count: Commentary=496.

Abbreviations: glutathione S-transferase (GST)

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COMMENTARY

      Understanding variability in semen analysis and the effects of any one contributing factor is exceedingly difficult given the multifactorial nature of the physiological process. Epidemiological issues such as insurance coverage, outpatient treatment settings and income bias makes assessing patient cohorts subject to a multitude of confounders. As such, Eisenberg *et al.* [1] should be commended for tackling this exceedingly difficult topic as they attempt to identify differences in semen quality that are attributable solely to race.

      The very notion that race plays a role in the quality of a man's sperm is controversial. With most cases of male infertility defined as idiopathic, recent estimates suggest that genetic abnormalities contribute 15-30% of male factor infertility [2]. It is thus tempting to speculate that certain genetic biomarkers [2] could be tied to race and used to predict fertility outcomes in general, and spermatogenesis, in particular.

      Xiao *et al.* [3] illustrate an example of this concept in a recent meta-analysis where the authors examined the expression of CAG-repeat length in the androgen receptor. Such tri-nucleotide-repeat disorders exhibit genetic anticipation in which the severity of the disorder is increased with successive generations. Long CAG repeat length has been postulated to affect male infertility; however, conflicting results have been reported [3]. Xiao *et al.* [3] found that increased CAG length was associated with male infertility in the Caucasian, but not the Asian populations.

      Ying *et al.* [4] highlighted further contributions of genetics to the differences between Asians and Caucasians. Their meta-analysis focused on the glutathione S-transferase (GST)

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family of genes that function as anti-oxidants in testicular tissues. Given that male germ cells are sensitive to oxidative stress through accelerated spermatozoal apoptosis, perturbations in any of the two major members of the GST family (GSTM1 an GSTT1) could theoretically influence male fertility. The homozygous deletion of these genes would abolish their activity with resultant elevated levels of oxidative stress inhibiting sperm health [4]. Interestingly, male infertility in *both* Caucasians and Asians was associated with the null genotype of GSTM1 while the null genotype of GSTT1 was associated with male infertility in only Asian men.

These aforementioned studies are interesting examples of how genetics may interact with race and fertility. As such, CAG repeat length and GSTM1/GSTT1 could be hypothesized to be rudimentary biomarkers for such findings. Eisenberg *et al.* [1] stress that their study was primarily designed to highlight racial differences rather than comprehensively characterize them. Indeed, this latter objective is nearly impossible to accomplish. Even in the context of genetics and race as highlighted in the studies above, common environmental factors such as exposure to air pollution can influence GSTM1 and GSTT1 genes [5] thus altering endpoints. Non-reported and occult conditions such as hypertension and visceral adiposity further cast bias onto the results given their influence on CAG repeat length [6]. With more data emerging about the multitude of influences on semen analysis, the concept of a race-based, or geographically based semen analysis reference ranges is something that should be considered.

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