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Evaluation of the impact of marijuana use on semen quality: a prospective analysis

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Abstract

Aims: To assess if marijuana consumption – prevalent among men of reproductive age and becoming widespread due to decriminalization – is associated with changes in semen parameters. Marijuana's active metabolite, tetrahydrocannabinol, can alter signaling pathways within spermatozoa, affecting spermatogenesis and fertility.

Methods: We prospectively evaluated semen analyses (SA) from men presenting for infertility evaluation at one institution from July 2017 to April 2018. Participants completed a reproductive health questionnaire including items regarding marijuana consumption. SA was performed in accordance with World Health Organization (WHO) 5th Edition criteria. SA parameters included volume (ml), concentration (million/ml), motility (%), progressive motility (%), and Tygerberg strict morphology (%).

Results: A total of 409 patients completed the questionnaire; 174 (43%) men reported marijuana use (ever-users). Current and past users comprised 71 (17%) and 103 (25%), respectively. Compared with never-users, current and past users had a significantly higher likelihood of abnormal sperm strict morphology (33.1% *versus* 50.7% and 53.4%, respectively; $p < 0.001$). However, sperm motility was more likely to be less than WHO reference values in never-users than current and past-users (38.3% *versus* 21.1% and 27.2%, respectively; $p = 0.01$). In multivariate logistic regression analyses, current use was associated with increased odds of abnormal strict morphology [odds ratio (OR) 2.15, 95% confidence interval (CI): 1.21–3.79] and semen volume less than WHO reference value (OR 2.76, 95%CI: 1.19–6.42), while odds of less than WHO reference value sperm motility were reduced (OR 0.47, 95%CI: 0.25–0.91).

Conclusion: Marijuana use is common among men presenting for fertility evaluation, and may have a detrimental effect on semen quality, particularly morphology and volume, but may be protective against abnormal sperm motility. Large, prospective studies of both semen quality and fertility in this growing, at-risk population are warranted.

Keywords: cannabis, male infertility, marijuana, reproductive health, semen analysis, spermatogenesis

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Introduction

Consumption of marijuana (*Cannabis sativa*) for medical and recreational purposes is rising globally. It is estimated that 192 million individuals, comprising 2.5% of the world population, reported marijuana use in 2016, making it the most commonly used drug worldwide.[1,2] In the United States (US), medical use of marijuana is legal in 33 states, and recreational use has been legalized in 11 states. According to the National Institute of Health, approximately 22 million Americans currently partake in marijuana use, with 30% of marijuana consumers meeting criteria for a substance use disorder.[3] In Washington state, 44% of individuals under age 29 report prior cannabis use.[4] Consumers in Washington

alone spent an estimated US $6.9 billion on legal marijuana products in 2016, a 34% rise from 2015.[4] Projections suggest that this industry will reach $21.6 billion by 2021.[4] States with more recent legalization are anticipated to experience similar demand and industry growth in the coming years. Given the widespread use and expanding decriminalization of marijuana, there is an increasing demand for a better understanding of its potential impacts on general and reproductive health, as well as public policy and global healthcare.

Cannabinoids have two major categories: exogenous, which are plant-based and include Δ9- tetrahydrocannabinol (THC), the psychoactive component of marijuana, and endogenous, which are synthesized by various tissues of the human body. Cannabinoids bind to cannabinoid-binding receptors (CB1 and CB2) located in the central and peripheral nervous systems, the anterior pituitary, and in reproductive organs and cells within, including spermatozoa.[5,6] Marijuana and its active metabolite, THC, can alter the signaling system within spermatozoa by competing with endogenous cannabinoids at CB receptors, potentially resulting in negative effects on spermatogenesis, sperm function, and male fertility.[7] *In vitro* studies have demonstrated a dose-dependent detrimental effect of THC on progressive sperm motility that becomes more pronounced as sperm quality declines.[7] Furthermore, spontaneous and artificially induced acrosome reactions are also inhibited by THC.[7]

Mouse studies have demonstrated ubiquitous presence of cannabinoid receptors in testicular somatic and germ cells.[8,9] Effects of THC on testis includes alterations in Sertoli cell signaling.[8,9] Additionally, decreases in sperm motility and, ultimately, fecundity, have also been observed.[10] Further, mice studies have found that endocannabinoids can promote meiotic progression of germ cells *via* the CB2/Type 2 cannabinoid receptors.[11,12] This indicates that cannabinoids may exert a significant effect on spermatogenesis, although the extent of that effect is still unclear. Stemming from earlier human studies,[5–7,13–17] two recent European population-based analyses described the negative effect of marijuana consumption on male reproductive health with an emphasis on semen quality.[18,19] However, a recent US single-center study demonstrated conflicting results regarding the effects of marijuana on male reproductive health, confirming higher sperm concentrations and total sperm counts in marijuana users compared with never-users.[20] Nassan *et al.* consider the likelihood of a dose-dependent, non-linear effect of marijuana, whereby low-to-moderate use of marijuana may be pro-spermatogenic, and higher doses produce adverse effects on semen parameters.[20]

Given the unclear and controversial impact of marijuana on male fertility and reproductive health, we sought to contribute further to this body of literature and ongoing polemic. The present study aims to investigate the effect of marijuana on semen parameters in a large cohort of men presenting to a high-volume male fertility center in a state (WA, USA) with legal recreational marijuana. We hypothesized that men who use marijuana have impaired semen quality when compared with those who do not consume marijuana. We aimed to characterize differences in semen quality between men who affirmatively reported consumption of marijuana compared with never-users.

Materials and methods

Study design and population

We conducted a prospective cross-sectional study between the months of July 2017 and April 2018. After Institutional Review Board approval and written informed consent from study participants, prospectively collected semen analyses (SA) were obtained from men who presented for infertility evaluation at the University of Washington (UW) Men's Health Center. A total of 409 participants completed SA and reproductive health questionnaires. A single semen sample was collected from each patient at the initial evaluation. Samples were obtained by having each patient masturbate and ejaculate into a sterile cup. Patients with azoospermia, genetic mutations, or other discrete, identifiable causes of infertility including varicocele and testicular atrophy were excluded. Patients provided at least one SA to the UW Male Fertility Lab (MFL) after completing a reproductive health questionnaire that included detailed queries regarding age, marijuana use history, including frequency and duration, and tobacco smoking history. Questions regarding current and past marijuana consumption were used to classify patients as never, current, or past-users. Past-use was defined as any marijuana use and a ⩾3-month-period of abstinence from marijuana consumption at time of SA. This interval was chosen to

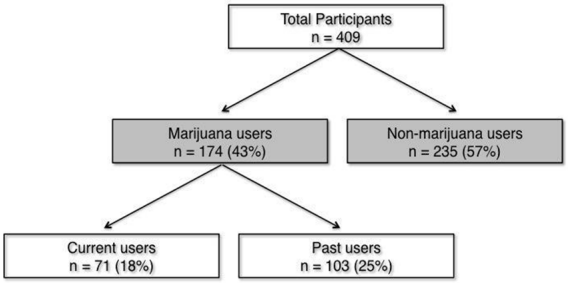

Figure 1. Flowchart of study participants.

ensure a full cycle of spermatogenesis after marijuana cessation. Precise quantification of marijuana use was not ascertained given the inability to standardize dosage of inhalation, ingestion, and transdermal forms of cannabis consumption.

A single SA per subject was utilized given the high proportion of patients presenting with reliable SA records from partnering reproductive endocrinology center-based andrology laboratories. Outside SA records were not included in the present analysis. Hormone panels were not routinely obtained, in keeping with guidelines for diagnostic evaluation of the infertile male by the American Society for Reproductive Medicine (ASRM) and the American Urological Association, which recommend against routine hormonal evaluation for normozoospermic men.[21,22]

SA was performed by the UW MFL in accordance with World Health Organization (WHO) 2010, 5th Edition guidelines.[22] SA parameters recorded for this study included volume (ml), concentration (million/ml), motility (%), progressive motility (%), and Tygerberg strict morphology (%).[22] Total motile count (TMC) and total progressive motile count (TPMC) were calculated by multiplying (volume × concentration × %motility) and (volume × concentration × %progressive motility), respectively. SA parameters were quantified into dichotomous variables defined as below or within WHO 2010, 5th Edition reference values (95%).

Patients with varicocele, genital infection, or who use any gonadotoxins were excluded from the study. Physical examination of each patient was conducted by a reproductive urologist.

Statistical analysis

Univariate comparisons of demographics and SA parameters with marijuana use (never, current, and past) were done using Chi-squared tests for categorical variables [smoking, body mass index (BMI), SA parameters as dichotomous within/below WHO reference value] and ANOVA for continuous variables (age, SA parameters as continuous). For each semen quality parameter, a multivariate logistic regression analysis adjusting for patient age, tobacco smoking status, and BMI was performed. Each model measured odds having a value that exceeded the WHO reference value for past/current-users compared with never-users. Statistical significance was defined by $p$value <0.05. All data analysis was performed using the statistical software Stata 14.0. Given the prospective cross-sectional nature of this study, statistically significant results are correlational and do not prove causation.

Results

Of the men included in our study, 174 (43%) reported marijuana use. Among marijuana users, current- and past-users comprised 71 (17%) and 103 (25%) individuals, respectively (Figure 1). Mean duration of marijuana use was 9.4 years. Mean ages were 35 and 36.3 years in the marijuana ever-users and never-users, respectively (Table 1). The majority of patients had BMI $\geqslant$25 in all groups; however, never-users were more likely to have healthy BMI (20–24.99) ($p<0.02$). Tobacco use was more common in marijuana current-users, although there were a large proportion of never-users without tobacco use data (Table 1).

Semen parameters, examined as continuous measures, were similar across user groups with the exception of a lower percent of strict morphology in the user groups ($p=0.007$, Table 1). Skewness in the continuous measures normal distribution resulted in differences in categorization of within/below WHO reference value across user groups despite similar means across the groups. Using the dichotomous SA parameters: normal (above/equal) or abnormal (below) the WHO 5th edition reference values [volume $\geqslant$1.5 ml), concentration $\geqslant$15 million/ml, motility $\geqslant$40%, progressive motility $\geqslant$32%, and Tygerberg strict morphology $\geqslant$4%]. Current users were more likely to have below WHO reference volume ($p=0.04$) and higher proportion with abnormal strict morphology ($p<0.001$), Marijuana never-users were more likely to have below WHO reference sperm motility when compared with ever-users ($p<0.001$).

Table 1. Participant data.

Variables	WHO reference ranges	Current *n* = 71 (17%)	Past *n* = 103 (25%)	Never *n* = 235 (57%)	p-value
Age in years (mean, SD)		34.8 (5.2)	35.0 (5.3)	36.3 (7.4)	0.39
BMI (kg/m^2)					
<20		2 (2.8)	5 (4.8)	1 (0.4)	<0.02
20–24.99		16 (22.5)	18 (17.5)	67 (28.5)	
⩾25		53 (74.7)	80 (77.7)	167 (71.1)	
Current tobacco use (%)					
No		44 (62.0)	78 (75.7)	167 (71.1)	<0.01
Yes		26 (36.6)	25 (24.3)	28 (11.9)	
Unknown		1 (1.4)	0 (0.0)	40 (17.0)	
Volume, mean (SD)	1.5–7.6 ml	3.2 (1.47)	3.13 (1.48)	3.03 (1.55)	0.68
Concentration, mean (SD)	15–259 million/ml	98.36 (96.08)	100.15 (92.76)	79.22 (75.07)	0.26
% Motility, mean (SD)	40–81 %	46.04 (21.66)	48.74 (15.91)	49.99 (18.69)	0.25
% Progressive motility, mean (SD)	31–75%	40.83 (19.73)	40.06 (16.67)	41.7 (18.66)	0.85
% Strict morphology, mean (SD)	4–48%	5.48 (4.19)	3.94 (3.65)	4.79 (4.71)	**0.007**
TMC, mean (SD)	>20 million	145.48 (174.97)	146.3 (150.29)	139 (169.51)	0.95
TPMC, mean (SD)	>12.5 million	128.15 (150.51)	123.59 (134.37)	121.48 (158.67)	0.93

BMI, body mass index; SD, standard deviation; TMC, total motile count; TPMC, total progressive motile count; WHO, World Health Organization.

In multivariate logistic regression analysis, both current and past users demonstrated significantly increased odds of having abnormal strict morphology [odds ratio (OR) 2.15, 95% confidence interval (CI), 1.21–3.79 and OR 2.26, 95% CI 1.37–3.73, respectively) (Table 2). Additionally, current users had significantly increased odds of having below WHO reference value semen volume (OR 2.76, 95% CI 1.19–6.42). Current users trended toward a greater odds of below WHO reference value TPMC (1.71, 95% CI 0.85–3.47); however, the significant threshold of $p = 0.05$ was not met. Current users had significantly reduced odds of having below WHO reference value total motility (OR 0.47, 95% CI 0.25–0.91). However, a significant difference was not found in regard to progressive motility.

Discussion

Marijuana is consumed widely among individuals of reproductive age, and its prevalence in North America is among the highest worldwide.[1–4] Despite the ubiquity of its use, the potential effects of marijuana on male reproductive health remain largely undefined. In our prospective cross-sectional study of 409 men presenting for fertility evaluation, we observed a high rate of marijuana use, with 43% of men reporting use. Consistent with our hypothesis, we found ever-users to have greater odds of below WHO reference value semen parameters including strict morphology and semen volume when compared with never-users. In contrast, odds of sperm motility within WHO reference values was greater among marijuana users, suggesting a protective effect.

Two recent European population-based studies examined the detrimental effect of marijuana use on male infertility with particular emphasis on semen quality.[18,19] In an unmatched case-controlled study of 318 men ⩽30 years old from the United Kingdom (UK), the authors found that marijuana use in the 3 months prior to SA

Table 2. Odds of SA parameter below WHO reference value for past and current users *versus* never-users.

	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Volume		
Never	Ref	Ref
Past	1.22 (0.55–2.73)	1.13 (0.46–2.77)
Current	2.55 (1.19–5.46)*	2.76 (1.19–6.42)*
Concentration		
Never	Ref	Ref
Past	2.08 (1.22–3.57)*	1.97 (0.94–4.12)
Current	2.32 (1.45–3.73)*	1.32 (0.66–2.66)
Motility (%)		
Never	Ref	Ref
Past	0.6 (0.36–1.0)	0.68 (0.4–1.16)
Current	0.43 (0.23–0.81)*	0.47 (0.25–0.91)*
Progressive motility (%)		
Never	Ref	Ref
Past	0.91 (0.55–1.51)	0.9 (0.53–1.54)
Current	0.7 (0.38–1.29)	0.67 (0.35–1.28)
Morphology (%)		
Never	Ref	Ref
Past	1.48 (0.76–2.89)*	2.26 (1.37–3.73)*
Current	2.15 (1.07–4.34)*	2.15 (1.21–3.79)*
TMC		
Never	Ref	Ref
Past	1.25 (0.68–2.3)	1.17 (0.61–2.23)
Current	1.35 (0.69–2.69)	1.33 (0.65–2.73)
TPMC		
Never	Ref	Ref
Past	1.59 (0.86–2.94)	1.34 (0.7–2.57)
Current	1.91 (0.98–3.75)	1.71 (0.85–3.47)

[a]Adjusted for age, smoking, and BMI.
*$p < 0.05$.
BMI, body mass index; CI, confidence interval; OR, odds ratio; Ref, reference; SA, semen analyses; SD, standard deviation; TMC, total motile count; TPMC, total progressive motile count; WHO, World Health Organization.

collection doubled the risk of poor morphology (<4% normal forms) when adjusting for other risk factors.[18] Limitations of this study include relatively small sample size and low participation rate among men eligible for the study. In a Danish study, Gundersen *et al.* evaluated semen quality of 1215 young men (18–28 years) exposed to marijuana and other recreational drugs in the past 3 months.[19] The authors found that routine use of marijuana (greater than once per week) was associated with a nearly 30% reduction in median sperm concentration and total sperm count after adjusting for confounding variables, including hours of abstinence prior to SA collection, sexually transmitted infections, and consumption of tobacco, alcohol, and other recreational drugs.[19] The effect was compounded by consumption of other recreational drugs, which further reduced sperm concentration and total sperm count by more than 50% from baseline when combined. Limitations of this study include reporting bias and lack of granularity regarding quantity of marijuana consumed and duration of abstinence.[19]

Nassan *et al.* published a conflicting report on the association of marijuana smoking and semen quality, sperm DNA fragmentation, and serum reproductive hormones.[20] The authors evaluated 662 subfertile men presenting to a fertility center located in a state with legalized recreational marijuana use (MA, USA). Subjects were of similar mean age and mean BMI to our cohort, although prevalence of marijuana use was higher (55%). The authors found that ever-users of marijuana had significantly higher mean sperm concentration (62.7 *versus* 45.4 million/ml, $p < 0.05$) and total sperm count (150 *versus* 114 million/ml, $p < 0.05$) than never users.[20] While statistically different, the clinical significance is less meaningful as both means are well within the range of normal as defined by WHO 2010, 5th Edition criteria.[23] Of perhaps greater consequence is the finding that a significantly greater proportion of marijuana never-smokers than ever-smokers had below WHO reference value semen parameters including concentration (12.4% *versus* 5.4%, $p < 0.01$), motility (41.6% *versus* 26.2%, $p < 0.01$), progressive motility (58.8% *versus* 48.3%, $p \leq 0.05$), and total sperm count (9.1% *versus* 3.3%, $p < 0.01$).[20] There was no appreciable difference between never-smokers and ever-smokers with regard to odds of abnormal strict morphology.

In our investigation, the prevalence of marijuana use among men presenting for infertility evaluation was 43%, which is comparable with marijuana use within the general population of Washington.[4] Among ever-users, past use was more common than current use (25% *versus* 17%, respectively). After adjusting for age, BMI, and tobacco use, ever-users were observed to be at significantly greater odds of having below WHO reference value sperm strict morphology and semen volume compared with never-users. Marijuana current-users had a two-fold increased risk of abnormal strict morphology, and, paradoxically, past-users had the highest odds of deficits in strict morphology, suggesting a delayed negative effect of marijuana on sperm morphology.

The importance of sperm morphology has been a subject of debate for several decades and continues to challenge clinicians counseling couples struggling with infertility. Certainly, patients should understand the role morphology may play in the potential for success with intrauterine insemination (IUI). Nikbakht and Saharkhiz determined normal sperm morphology to be a prognostic factor for IUI cycle success.[24] Furthermore, a recent systematic review and meta-analysis of IUI cycle outcomes in men with and without teratozoospermia (4% or less normal forms) demonstrated a trend toward a lower rate of ultrasound-verified pregnancies per IUI cycle (12.1% *versus* 14.2%, $p = 0.06$), although this did not reach statistical significance.[25] Therefore, it is our strong recommendation to patients with teratozoospermia to cease use of marijuana while fertility remains a concern.

We also identified a trend toward a greater odds of below WHO reference value sperm concentration in past users, and an almost three times increased risk of low semen volume. When combined, these reduced parameters can precipitate a relative decline in TMC, as evidenced by the trend toward abnormal TMC in our cohort of marijuana users. TMC has been suggested to be the most critical indicator of severity of male infertility and is of particular importance to couples attempting IUI.[26,27] We therefore advise against marijuana use in men with reduced TMC, particularly if attempting IUI.

In contrast to the detrimental effect of marijuana use we observed on other semen parameters, our cohort of users had significantly greater chances of sperm motility within WHO reference range and trended toward improved odds of normal progressive motility. Specifically, current users

had a two-fold likelihood of sperm motility surpassing WHO reference range than non-users. This suggests a partially pro-spermatogenic effect also observed by Nassan *et al.*,[20] the mechanism of which is not apparent. In fact, translational studies have demonstrated contrasting results whereby cannabis exposure leads to sperm mitochondrial dysfunction and, thus, motility impairment.[28,29] The mechanism by which human sperm motility is preserved, and potentially improved, by cannabis exposure, requires further study.

One potential limitation of this study is that subject recruitment was limited to a single center in Washington state where marijuana is legal for recreational use, thus limiting the generalizability to the entire US population. Our study evaluates subjects from a single fertility center. This is a limitation of our study as it has the potential to lead to selection bias.

Additionally, while we did exclude patients with discrete, identifiable causes of infertility such as varicocele, testicular atrophy, known genetic causes of infertility, other exposures such as gonadotoxic pharmaceuticals/medical treatments, chemicals, or heat are subject to reporting bias on the part of the patient. Additionally, other exposures such as dietary choices, control of sleep apnea, exercise frequency, and duration were not able to be controlled for. Finally, our study has a potential limitation in that we did not ask subjects about the use of other recreational drugs, including opioids. We believe that the literature would benefit from additional studies looking at other recreational drug use.

Our study did not evaluate testicular function by way of testosterone and gonadotropin assays. Because collection of hormonal data is performed only in the setting of abnormal semen parameters, per ASRM guidelines, we elected to include participants with and without need for hormonal evaluation.[21] Additionally, use of a single SA can be regarded as a limitation. However, many participants presented with previously obtained, reliable SA, allowing clinical fertility evaluation per ASRM guidelines. The authors did not feel it reasonable to subject participants to tertiary semen collections, which can be distressing, logistically taxing, and costly.

Like any prospective study in this area, our ability to determine precise quantification of marijuana consumption is limited by inability to standardize dosage in inhalation, ingestion, and transdermal forms of cannabis. Because definitions like "daily use" have high variability in actual levels of consumption, we elected to forgo attempts at quantification.

When taken as a whole, our investigation, along with previously published reports, confirm the complex interactions marijuana may have with the male reproductive system and subsequent impacts on sperm function.[30,31] We found a distinct detrimental effect on sperm morphology and volume, and signals of deleterious effects on TMC and TPMC. While this discourse continues, it is important to account for reporting bias, which may explain the discrepancies between studies, particularly given the legal status of marijuana in each site of study. Additionally, the ability of patients to accurately recall marijuana usage, and for investigators to adequately quantify use, are also important limitations to this field of study. Significant breakthroughs in this area of study will require additional means of clarifying marijuana use, such as hair drug screening.

In our study, we found that marijuana consumption had a mixed impact on sperm quality in reproductive-age men presenting for infertility evaluation. These findings are of critical importance in an era where marijuana use has been widely legalized in the US for both medical and recreational purposes, despite a paucity of contemporary data on its deleterious impact on semen quality and overall reproductive health. Further large-scale, randomized studies are prerequisite to fully understanding the association between marijuana use and male reproductive health.

Conclusions

Marijuana use is common among men presenting for infertility evaluation and may have a detrimental effect on semen quality, particularly sperm strict morphology and semen volume, as well as a signal of diminished TMC and TPMC. Use of marijuana may not have negative effects on sperm motility but may even improve it. This positive finding is specific to motility. Given these findings, large, prospective studies of both semen quality, fertility, and pregnancy outcomes in this growing, at-risk population are warranted.

Conflict of interest statement

The author(s) declare that there is no conflict of interest.

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Ethics statement

This study was approved by the University of Washington IRB (approval number STUDY00004826). Written informed consent was obtained from all participants.

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