

# Cocaine Use in the Infertile Male Population: A Marker for Conditions Resulting in Subfertility

Mary K. Samplaski<sup>a</sup>   Bassel G. Bachir<sup>a</sup>   Kirk C. Lo<sup>a, b</sup>  
Ethan D. Grober<sup>a</sup>   Susan Lau<sup>a</sup>   Keith A. Jarvi<sup>a, b, c</sup>

<sup>a</sup>Division of Urology, Department of Surgery, Mount Sinai Hospital, University of Toronto; <sup>b</sup>Faculty of Medicine, Institute of Medical Science, University of Toronto; <sup>c</sup>Lunenfeld Tannenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada

## Key Words

Cocaine • Substance abuse • Infection • Male fertility • Semen

## Abstract

**Introduction:** We sought to evaluate the incidence and effect of cocaine use in the infertile male population. **Materials and Methods:** Men presenting for fertility evaluation reporting cocaine usage were identified via prospectively collected database. Data were analyzed for usage patterns, reproductive history, associated drug use and medical conditions, hormonal and semen parameters. **Results:** Thirty-eight out of 4,400 (0.9%) men reported cocaine use. Most used cocaine every 3 months or less. Compared with non-cocaine using men, cocaine users reported more recreational drug use (89 vs. 9.2%), marijuana use (78.9 vs. 11.4%), chlamydia (10.5 vs. 3%), herpes (7.9 vs. 2.5%), and tobacco use (55.3 vs. 19.5%). After excluding men with causes for azoospermia, the mean semen parameters for cocaine users were: volume  $2.47 \pm 1.02$  ml; concentration  $53.55 \pm 84.04 \times 10^6$ /ml; motility  $15.72 \pm 12.26\%$ ; total motile sperm count  $76.67 \pm 180.30 \times 10^6$ . **Conclusions:** Few (< 1%) men in our infertile population reported the use of cocaine, and the frequency of use was low. Given the low use rates and limitations of reporting bias, it is difficult to determine the direct effect of cocaine use on male fertility. However, while infrequent cocaine use seems to have limited impact on semen parameters, men reporting cocaine use represent a different cohort of men than the overall infertile population, with higher rates of concurrent

substance abuse, tobacco use and infections, all of which may negatively impact their fertility. Reported cocaine users should be screened for concurrent drug use and infections.

Copyright © 2014 S. Karger AG, Basel

## Introduction

The United States is the world's largest consumer of cocaine [1]. Cocaine is commonly used in upper-middle class communities. In addition, there seems to be a male predominance for usage, with the ratio of male to female users being approximately 3.8:1 [2].

Some recreational drugs have been shown to negatively impact male fertility, including marijuana [3] and tobacco [4]. However, there is only 1 published study on the effects of cocaine on male fertility [5]. Animal models have demonstrated that chronic cocaine usage in male rats results in seminiferous tubule degeneration [6], reduced pregnancy rates [7], and a decrease in mature spermatogenic forms [7]. The single published human study demonstrates that cocaine use was associated with a sperm concentration of  $< 20 \times 10^6$ /ml [5]. There have been no studies published on the use and effect of cocaine in infertile men. We sought to evaluate the incidence of cocaine use in the infertile male population, usage patterns and associated conditions, and if cocaine use is associated with changes in human male hormonal and semen parameters.

**Table 1.** Frequency of concurrent substance abuse and infections in men reporting cocaine use at presentation for fertility evaluation versus the general population

Parameter	Infertile male cocaine users (n = 38)	Infertile male population (n = 4,400)	p value
Genitourinary infection	31.6% (n = 12)	18.8% [17]	0.115
Chlamydia	10.5% (n = 4)	3% (n = 132)	0.012
Gonorrhea	2.6% (n = 1)	2% (n = 90)	0.803
Herpes	7.9% (n = 3)	2.5% (n = 111)	0.048
Bladder infection	7.9% (n = 3)	5.2% (n = 228)	0.482
Testis infection	2.6% (n = 1)	2.3% (n = 102)	0.899
Penis infection	2.6% (n = 1)	2.1% (n = 92)	0.821
Illicit drug* use overall	89% (n = 34)	9.2% [16]	< 0.001
Marijuana	78.9% (n = 30)	11.4% (n = 501)	< 0.001
Alcohol	50% (n = 19)	51.6% (n = 2,271)	0.909
Tobacco	55.3% (n = 21)	19.5% (n = 860)	< 0.001

\*Includes marijuana, anabolic steroids, LSD, heroin, ecstasy

## Materials and Methods

Men presenting for a fertility evaluation from 2003 to 2013 at a single male infertility specialty clinic, who self-reported cocaine use were identified via a prospectively collected database. The frequency of cocaine use was also patient recorded. Patients also reported other substances used, as well as prior medical and reproductive history. All of these reported answers were confirmed by the interviewing physician. The collection and analysis of data in this database was approved by the Research Ethics Board of the Mount Sinai Hospital.

Data were analyzed for patient age, reproductive and medical history, substance use history, hormonal, and semen analysis parameters. Semen samples were collected at several laboratories, based on patient convenience. Semen samples were collected between 2 and 5 days after the last ejaculation. Semen samples were assessed for volume and then analyzed for sperm count, sperm concentration, and motility by computer-assisted semen analysis following the 2001 WHO criteria. All andrology laboratories used validated methodologies and performed their own quality control procedures. Sperm morphology was assessed using the WHO criteria. These criteria are based on microscopic high-power evaluation of 200 sperm for intactness of membranes of acrosome, head, neck, midpiece and tail.

For comparing semen and parameters mean  $\pm$  SD was used. For contingency tables, the chi-squared test was used, with  $p < 0.05$  considered as significant.

## Results

From 2003 to 2013, 38/4,400 men (0.9%) reported using cocaine. The mean age of men reporting cocaine use was  $38.2 \pm 8.1$  years. Among users, the frequency of use was quite low with only 1 man (2.6%) reporting using

cocaine weekly, 4 men (10.5%) reporting using cocaine monthly and the rest (n = 33, 86.8%) reporting cocaine use every 3 months or less.

There was a relatively high incidence of reported prior genitourinary infections in 13/38 (34.2%) men reporting cocaine use (table 1), including: chlamydia (n = 4, 10.5%), herpes (n = 3, 7.9%), bladder infection (n = 3, 7.9%), gonorrhea (n = 1, 2.6%), testis infection (n = 1, 2.6%) and penis infection (n = 1, 2.6%). This was generally lower than reported infection rates in our non-cocaine using population of infertile males, who had an overall incidence of reported history or genitourinary infections of 826/4,400 (18.8%), specifically chlamydia (n = 132, 3%), herpes (n = 111, 2.5%), bladder infection (n = 228, 5.2%), gonorrhea (n = 90, 2%), testis infection (n = 102, 2.3%), and penis infection (n = 92, 2.1%). While all of the infection rates were lower in non-cocaine using men, only the reported rates of chlamydia ( $p = 0.012$ ) and herpes ( $p = 0.048$ ) were statistically significantly different between cocaine users and non-users.

Men reporting cocaine use also reported other health issues, some of which likely contributed to the infertility: 4 men (10.5%) reported a history of oncologic malignancy, including testis cancer (n = 2), non-Hodgkin's lymphoma (n = 1) and colon cancer (n = 1). Other health issues reported included depression (n = 3, 7.9%), asthma (n = 1, 2.6%), epilepsy (n = 1, 2.6%), spinal cord injury (n = 1, 2.6%) and diabetes (n = 1, 2.6%). The man with diabetes was a longstanding type-2 diabetic, with retrograde ejaculation. After trying cocaine for the first time (not medically endorsed) he had his first antegrade ejac-

ulation in many years, with a total sperm count (TSC) of  $131 \times 10^6$ . One man was seen for anejaculation from a spinal cord injury, although he did not report a similar effect after trying cocaine (also not medically endorsed).

Concurrent reported drug use was reported in 89% of the men compared with 9.2% in the male infertility population ( $p < 0.001$ ) (table 1). Reported substances used included marijuana, heroin, ecstasy, lysergic acid diethylamide (LSD), and anabolic steroids for bodybuilding. The most commonly reported other substance was marijuana, with 30 men (78.9%) reporting use (frequency of use not reported). One man (2.6%) reported heroin use, 9 men (23.7%) reported using ecstasy, 2 men (5.3%) reported LSD use, and 3 men (7.9%) reported using anabolic steroids for bodybuilding. Due to the small reported use rates for other substances, and also unknown effect on male fertility, we only chose to directly compare the use of marijuana between cocaine using and non-cocaine using men. For marijuana, the reported use rate in non-cocaine using infertile men was significantly lower at 11.4% ( $p < 0.001$ ).

Cigarette smoking was also more common in men who reported the use of cocaine, 55.3% (21/38) versus 19.5% (860/4,400),  $p < 0.001$ . Among cocaine using men, the reported frequency of tobacco use was: < 1 pack per day: 14/38, 66.7%, 1 pack per day: 6/38, 28.6%, 2 packs per day: 1/38, 4.7%. Interestingly, alcohol use was not more common among the men who reported cocaine use than the rest of our infertile men, with 19/38 men (50%) reporting that they drink alcohol, compared with 2,271/4,400 (51.6%) of non-cocaine using infertile men.

There were a number of other clear causes for infertility in men using cocaine, including 5 (13.2%) men who were undergoing consultation for vasectomy reversals, 4 men (10.5%) who had oncologic therapies rendering them azoospermic, 1 man (2.6%) with congenital epididymal obstruction and 2 men (5.2%) who were seen for biopsy-proven early maturation arrest. Semen samples were obtained on 18 men. It was unclear how many of these men were still taking cocaine at the time of semen analysis, as well as the timing of last cocaine usage to semen analysis. After excluding men with obstructive azoospermia, prior oncologic therapies rendering them azoospermic, known maturation arrest, and those using anabolic steroids, 11 men had semen analyses available for analyses. For men with more than one semen analysis, results were averaged. For these men, apart from sperm motility, the mean semen parameters were within the normal range: ejaculate volume  $2.47 \pm 1.02$  ml; sperm concentration  $53.55 \pm 84.04 \times 10^6/\text{ml}$  and motility

$15.72 \pm 12.26\%$ . One man had > 10 polymorphs per high powered field, suggestive of inflammation.

Two men reported discontinuation of cocaine and having semen analyses checked before and after discontinuation. For these men, the mean semen parameters before cocaine cessation were: ejaculate volume  $3.5 \pm 2.4$  ml; sperm concentration  $5.9 \pm 0.14 \times 10^6/\text{ml}$ ; motility  $50 \pm 0\%$ ; TSC  $140.7 \pm 22.49 \times 10^6$ . After cessation the mean semen parameters were: ejaculate volume  $3.75 \pm 1.06$  ml; sperm concentration  $25.65 \pm 16.48 \times 10^6/\text{ml}$ ; motility  $26 \pm 16.97\%$ ; TSC  $34.83 \pm 40.94 \times 10^6$ . The duration that semen parameters were checked after cocaine cessation was not recorded. With only 2 men having true semen testing before and after cocaine cessation, substantial conclusions cannot be made, however it is interesting to note that there in both men there was improvement in the sperm concentration.

Twenty-eight men had serum hormone levels checked. Again the exact relationship between the timing of cocaine usage and hormonal analysis could not be determined in these men. After excluding men who were taking exogenous testosterone and men with documented testicular failure, 8 men had hormonal testing. For these men, the mean FSH was  $10.8 \pm 5.7$  IU/l, LH  $7.8 \pm 4.7$  IU/l and testosterone  $16.1 \pm 7.1$  nmol/l.

## Discussion

The United States is the world's largest consumer of cocaine [1]. In 2008, approximately 88% of those who used cocaine were between 15 and 34 years of age [2]. There seems to be a male predominance for usage, with the ratio of male to female users reported as 3.8:1 [2]. In 2008, the lifetime prevalence of cocaine use among 50 year-olds reached 40% [8]. Some recreational drugs have been shown to negatively impact male fertility, including marijuana [3] and tobacco [4]. However, there is only 1 published study on the effects of cocaine on male fertility, and this was not in the infertile male population [5]. In light of these factors, we sought to evaluate the incidence of cocaine use in the infertile male population and its effect on male fertility.

We found that overall very few of our men admitted to the current use of cocaine (< 0.9%). This is much less than reported in the US literature, but similar to the Canadian literature. The US National Survey of Drug Use and Health estimates for 2009 reported that for people aged 26–34 years, 35–49 years, and 50 years and older, the prevalence of cocaine use in the past year was 4.2,

2.2, and 1%, respectively [8]. This is higher than Canadian reported cocaine usage rates, and according to the 2011 Canadian Alcohol and Drug Use Monitoring Survey, reported cocaine use in the past year was 0.9%, although this was not broken down by age [9]. The vast majority of our men reported cocaine use every 3 months or less, with 10.5% using monthly and only 1 man reporting use weekly. It is possible that the true incidence of use is higher, and our data are subject to reporting bias, given that cocaine is an illegal substance.

Biologically, cocaine is a nonspecific voltage gated sodium channel blocker [10]. Unlike most molecules, cocaine has pockets of both high hydrophilic and lipophilic efficiency, allowing it to cross the blood-brain barrier relatively easily [11]. Whether this dual hydrophilic and lipophilic nature allows it to also cross the blood-testis-barrier has not been studied. Well-established side effects of chronic cocaine use include depression, hemoptysis, bronchospasm, pruritus, gastrointestinal complications, bruxism, renal disease [12], and an increased of developing rare autoimmune or connective tissue diseases [13]. However, its effect on human male semen and hormonal parameters is unknown.

Most of what is known about the effects of cocaine on male reproductive function is from animal studies. One of these [7] looked at rats which were given chronic high-dose cocaine and then mated with female rats. Rats receiving cocaine had a pregnancy rate of 33 versus 86% for the controls ( $p < 0.05$ ), and offspring had lowered birth weights ( $p < 0.05$ ). Morphometric analysis showed a decrease in seminiferous tubule diameter in cocaine treated rats, as well as a reduction in the thickness of the germinal epithelium, and a decreased number of spermatids. Follow-up studies identified a testicular tissue protein that binds cocaine (although this protein was not defined) [14], and that the mechanism of cocaine induced testicular damage may be related to apoptosis [15]. Finally, an Iowa group looked at the morphometric testicular structure in rats treated with moderate to high doses of cocaine. Cocaine produced a rapid disruption of spermatogenesis with a 50% decrease in the number of normal seminiferous tubules, an overall reduction in the volume of seminiferous tubules, and also negative ultrastructural changes in the spermatogonia, spermatids, and Sertoli cells [6]. While most of these studies involved moderate to high doses of cocaine use (different than reported usage rates in our men), they do suggest that cocaine can indeed cross the blood-testis-barrier, and the testis may be susceptible to the effects of cocaine.

Similar studies to these have not been performed in humans, for obvious reasons. The only study in humans on the effect of cocaine on sperm parameters was performed by Bracken et al. [5] in 1990, which showed that men with sperm concentration  $< 20 \times 10^6/\text{ml}$  were twice as likely to have used cocaine within 2 years compared with men with higher sperm concentrations. Longer durations of cocaine use were associated with lower sperm motility and more abnormal forms. However, in our series, men using cocaine are more likely to use other substances, be smokers and have a history of sexually transmitted diseases, all of which are known to affect fertility. The true direct effect of cocaine on male fertility remains unknown.

Our data would suggest that at the relatively low frequency of cocaine usage that our patients report, cocaine seems to have limited impact on semen parameters. However, the men using cocaine represent a high-risk group for the use of other illicit drugs, some genitourinary infections and cigarette smoking (table 1), all of which have been shown to negatively impact male fertility.

We identified a relatively high incidence of reported prior genitourinary infections of 31.6% of infertile men using cocaine. While the overall reported incidence of reported genitourinary infections was not different among cocaine using and non-cocaine using infertile men, the incidence of some individual infections (chlamydia and herpes) was different, suggesting that infertile men using cocaine may have higher rates of sexually transmitted infections. As such, these men represent a population who should be aggressively screened for sexually transmitted infections, as these may impair fertility.

We also identified a higher rate of illegal drug use in men reporting cocaine use than that seen in the general population. A recently released report by the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration reported that for persons aged 12 and older in 2012, the rate of illicit drug use was 9.2% [16], compared with 89% of our men. The most commonly reported concurrently used drugs were marijuana and tobacco, and when compared with the general infertile male population, our cohort also reported a significantly higher use rate of marijuana (78.9 vs. 11.4%,  $p < 0.001$ ) and tobacco (55.3 vs. 19.5%,  $p < 0.001$ ) (table 1). Both of these substances have been shown to negatively impact male fertility [3, 4]. The impact on fertility of some of the other substances used by our patients, including heroin, ecstasy and LSD remains unknown.

Interestingly, 5 of the men were seen for vasectomy reversal consultation. Given the effects of cocaine on the cardiovascular and pulmonary systems, these men should be advised cessation prior to surgery, and anesthetic teams advised to avoid any adverse intraoperative events related to cocaine use.

Limitations of our study include the possibility of reporting bias, especially pertinent for an illegal substance. Additionally, for most men we did not know the timing between cocaine usage and semen and hormonal testing. It is possible that there is an acute effect that is not captured if semen is not checked shortly after usage. In addition, it is possible that the gonadotoxic effects seen in animal models would be seen in our patients if they used cocaine more frequently or at higher doses; most of our men only used cocaine every 3 months or less, less than in the animal studies. Finally, we do not have data on pregnancy and live birth rates in these men.

## Conclusions

Cocaine use is uncommon in our infertile male population (< 1%) and among users is infrequently used. Semen parameters among the cocaine users were close to normal with only the sperm motility being reduced. Given the low use rates and limitations of reporting bias, it is difficult to determine the true effect of cocaine use on male fertility. However, men who report the use of cocaine have higher reported rates of other substance use, cigarette use and histories of some genitourinary infections than the rest of the infertile men. Men reporting cocaine use represent a different cohort of men than the general infertile male population and should be screened aggressively for concurrent substance abuse and infections, both of which may negatively impact their fertility. While the effect of infrequent use of cocaine in these men likely plays a minimal role in their fertility at the low doses reported in our study, the concurrent drug use and infections may negatively impact male fertility.

## References

- 1 The World Factbook: Field Listing: illicit drugs. Central Intelligence Agency, 2008.
- 2 The State of the Drugs Problem in Europe 2008. Luxembourg, European Monitoring Centre for Drugs and Drug Addiction, 2008, pp58–62.
- 3 Rossato M: Endocannabinoids, sperm functions and energy metabolism. *Mol Cell Endocrinol* 2008;286(1–2 suppl):S31–35.
- 4 Tawadrous GA, Aziz AA, Mostafa T: Effect of smoking status on seminal parameters and apoptotic markers in infertile men. *J Urol* 2011;186:1986–1990.
- 5 Bracken MB, Eskenazi B, Sachse K, McSharry JE, Hellenbrand K, Leo-Summers L: Association of cocaine use with sperm concentration, motility, and morphology. *Fertil Steril* 1990;53:315–322.
- 6 Rodriguez MC, Sanchez-Yague J, Paniagua R: Effects of cocaine on testicular structure in the rat. *Reprod Toxicol* 1992;6:51–55.
- 7 George VK, Li H, Teloken C, Grignon DJ, Lawrence WD, Dhabuwala CB: Effects of long-term cocaine exposure on spermatogenesis and fertility in peripubertal male rats. *J Urol* 1996;155:327–331.
- 8 Fronczak CM, Kim ED, Barqawi AB: The insults of illicit drug use on male fertility. *J Androl* 2012;33:515–528.
- 9 Health Canada: Canadian Alcohol and Drug Use Monitoring Survey, 2011.
- 10 O’Leary ME, Hancox JC: Role of voltage-gated sodium, potassium and calcium channels in the development of cocaine-associated cardiac arrhythmias. *Br J Clin Pharmacol* 2010;69:427–442.
- 11 Dietrich JB: Alteration of blood-brain barrier function by methamphetamine and cocaine. *Cell Tissue Res* 2009;336:385–392.
- 12 Peces R, Navascues RA, Baltar J, Seco M, Alvarez J: Antiglomerular basement membrane antibody-mediated glomerulonephritis after intranasal cocaine use. *Nephron* 1999; 81:434–438.
- 13 Trozak DJ, Gould WM: Cocaine abuse and connective tissue disease. *J Am Acad Dermatol* 1984;10:525.
- 14 Li H, George VK, Crossland WJ, Anderson GF, Dhabuwala CB: Characterization of cocaine binding sites in the rat testes. *J Urol* 1997;158:962–965.
- 15 Li H, Jiang Y, Rajpurkar A, Dunbar JC, Dhabuwala CB: Cocaine induced apoptosis in rat testes. *J Urol* 1999;162:213–216.
- 16 U.S. Department of Health and Human Services: Results from the 2012 National Survey on Drug Use and Health: summary of national findings. Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2013.
- 17 Domes T, Lo KC, Grober ED, Mullen JB, Mazzulli T, Jarvi K: The utility and cost of Chlamydia trachomatis and Neisseria gonorrhoeae screening of a male infertility population. *Fertil Steril* 2012;97:299–305.