Recreational drugs and male fertility

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In this article, the authors explore the impact of modifiable factors such as smoking, alcohol and substance abuse on male reproductive health.

Lifestyle choices such as diet, nutritional supplements, exercise habits, body weight, smoking habits and recreational drug use influence overall health and wellbeing. The relationship between lifestyle factors and adverse effects on human reproductive health is widely debated in the scientific literature. One in seven couples in the UK is affected by infertility and a male factor is implicated in 30 per cent of these (Figure 1).[1]

SMOKING (NICOTINE) AND MALE FERTILITY

Tobacco smoking is the most prevalent lifestyle habit in society. Around 35 per cent of men of reproductive age smoke. Cigarette smoking has been well established as a significant health risk and features in around 13 per cent of cases of subfertility in both men and women.[2] Considering its multiple health risks, couples should be encouraged to give up smoking irrespective of fertility and pregnancy issues.

Quantifying a 'safe' or 'detrimental' level of cigarette smoking is still unclear. Heavy smoking (>20 cigarettes/day) is certainly associated with negative trends in sperm parameters. Smoking has been reported to cause an increase in serum gonadotrophins and a decrease in serum testosterone levels. It tends to affect all aspects of the semen parameters, including sperm concentration, density, motility and morphology.[3]

Smoking has been associated with increased aneuploidy and oxidative damage to the sperm DNA, secondary to reduced seminal plasma antioxidant levels.[4] This could in itself influence the probability

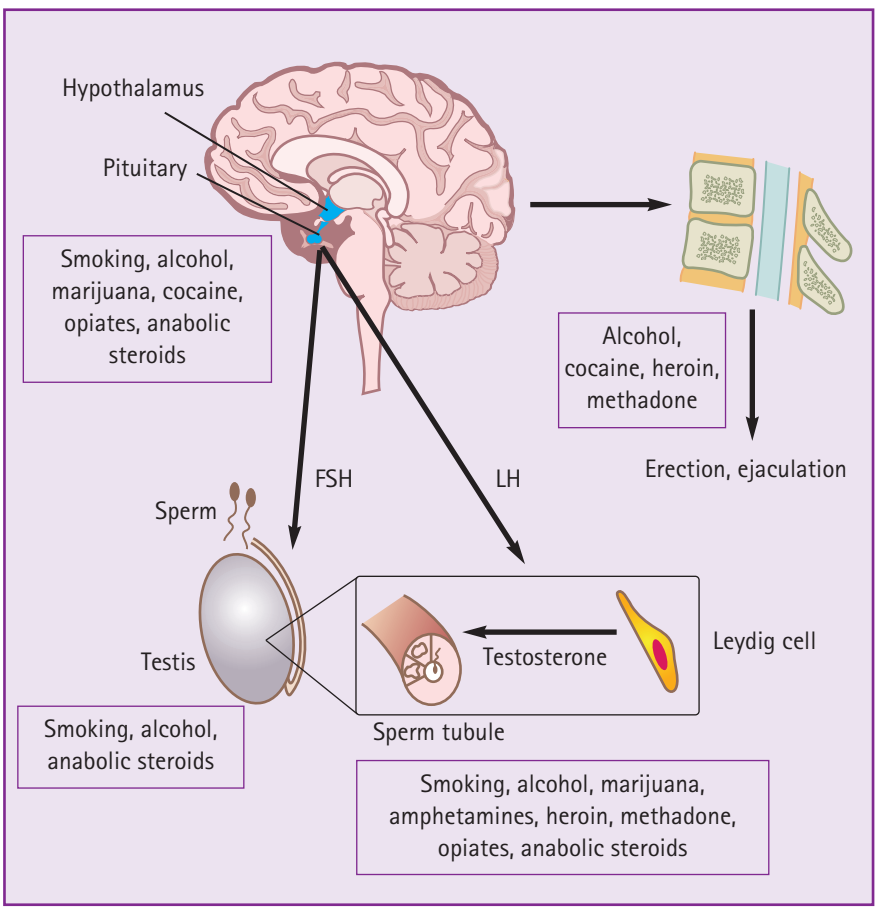

Figure 1. Different levels at which substance misuse could affect male fertility

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of conception. It has been suggested that smoking could also reduce mitochondrial activity in sperm and hence reduce their capacity to achieve fertilisation.[3,4]

There is emerging evidence to suggest that maternal smoking during pregnancy can affect the adult semen parameters of the male fetus, but the effect on the male offspring's reproductive function secondary to paternal smoking still remains unproven.[5] Smoking not only induces DNA damage in sperm,[6,7] but paternal smoking has also been associated with DNA damage in the cord blood of the offspring, an increase in miscarriage of the partner, congenital malformations and low birth weight of the fetus.

The evidence regarding effects of tobacco smoking on male fertility has been inconsistent in spite of the various mechanisms suggested. A recent multicentre case study has established that, although cigarette smoking may be associated with minor changes in motile sperm concentration, the evidence supporting its effect on fertility is lacking.[8] A meta-analysis of 21 cases demonstrated significantly lower rates of clinical pregnancy and live birth per cycle of assisted reproduction in women who were smokers as compared to non-smokers. However, the review showed conflicting evidence of the effect of male smoking on clinical pregnancy rates and no evidence to support reductions in fertilisation rates or live birth rates.[7]

Delaying fertility treatment to make lifestyle changes in men is unlikely to offer any benefit in improving outcomes of treatment. That men should stop smoking to improve their fertility is good practice rather than evidence-based advice.[2,6]

ALCOHOL AND MALE FERTILITY

The degree of negative impact that alcohol has on male reproductive function and quantifying the dose-dependent relationship is still not clearly understood.[3] The detrimental effects of alcohol are understood to be centrally as well as locally acting, at the testicular level. Alcohol impairs serum luteinising hormone (LH) and follicle-stimulating hormone (FSH) secretion, causes reduced LH biological activity and has also been associated with hypotestosteronaemia, which in turn can lower seminal plasma volume. There may also be an associated loss of secondary sexual characteristics, testicular atrophy, decreased libido and erectile dysfunction (see Figure 1).[3,9]

The association between alcohol and liver disease is well established. Studies have suggested that testicular spermatogenesis is more sensitive to alcohol damage than liver tissue. Heavy and prolonged alcohol consumption can be detrimental to sperm, as was shown by a study in which men who were drinking heavily for five days a week, for at least a year, were compared with men who never drank. Heavy alcohol consumption can lead to primary testicular failure causing partial or complete arrest of spermatogenesis. The mechanism is not yet clear but may be secondary to oxidative stress.[3,9]

Acute or chronic alcohol intake has been associated with increased serum beta-endorphin levels. This not only suppresses the hypothalamic-pituitary-testicular axis but also reduces testosterone production and its release from the testis. Raised inflammatory cells are not uncommon in the seminal fluid of heavy alcohol consumers. This is a sign of irritative prostatitis and can result in asthenospermia.

The impact of alcohol cessation on the reversal of any of these effects is conflicting. Studies conducted on the mouse model have shown a partial recovery of semen parameters on discontinuation of alcohol. A six-year follow-up report of a male patient's semen parameters secondary to heavy chronic alcohol abuse showed gradual worsening, ultimately resulting in azoospermia. Testicular biopsy confirmed arrest of the germinal cells. These findings were dramatically reversed, with completely normal sperm parameters evident within three months of alcohol withdrawal.[10]

It has been implicated that genetic background as well as nutritional status can modify alcohol-induced spermatogenesis. An autopsy study suggested that having the glutathione S-transferase M1 genotype offers protection from alcohol-induced sperm abnormalities. Nutritional deficiencies, including those of protein, folate, vitamins A, D, E, B_{12} and minerals such as magnesium and zinc may potentiate the toxic effects of alcohol.[9]

A multicentre prospective study showed that men who had one additional drink per day had a greater than two-fold increased risk of not achieving a live birth with assisted reproductive techniques (ART), depending on the time period of alcohol consumption. Alcohol consumption within a month of the ART cycle in men was also associated with a 2.7–38.0 times increased risk of miscarriage.[11,12] It has been suggested that consumption of more than one unit of alcohol per day can reduce the effectiveness of ART procedures.[1]

The body of evidence associating alcohol with reduced male fertility is insufficient. Though alcohol has been implicated adversely to affect all sperm parameters causing oligo-, astheno- and teratozoo-spermia, a univariate analysis suggested that drinking alcohol was not related to low motile sperm concentrations but in fact showed a protective effect compared to men who reported no alcohol consumption within 91 days prior to semen analysis. Men should be advised to refrain from heavy alcohol intake, but limiting alcohol intake to less than three to four units per day is unlikely to affect semen parameters and fertility.[1]

RECREATIONAL SUBSTANCE MISUSE

Ethical issues have surrounded prospective studies on the effects of illicit drugs on humans because of the illegal nature of these substances and their dangerous side-effects. This has made it difficult to establish a clear relationship between their consumption and human fertility. The evidence available to date suggests a negative impact.

Marijuana/cannabis

Marijuana is one of the most frequently misused substances. It suppresses male fertility through central and peripheral actions. The serum LH level is reduced, leading to a dose-dependent suppression of testosterone release from the Leydig cells. These, in turn, suppress spermatogenesis and cause oligospermia.[13] Marijuana contains cannabinoids, which bind to receptors on the ductus deferens and the sperm. Activation of the endocannabinoid receptors on sperm causes dose-dependent asthenospermia as well as inhibition of sperm capacitation and the acrosome reaction at fertilisation. Cannabinoids also promote Sertoli cell apoptosis.

Interestingly, cannabinoids have a biphasic action: at lower levels (commonly seen with endogenously produced endocannabinoids) they promote sperm activity, while at high levels (as seen with marijuana abuse) sperm function is inhibited.[13]

Cocaine

The teratogenic effects of cocaine abuse by women during pregnancy are well known. Cocaine has significant systemic and cardiovascular effects in both the mother and the fetus. Perinatal cocaine use is associated with increased risk of miscarriage, preterm labour, preterm premature rupture of membranes, placental abruption and fetal growth restriction. Neonatal abnormalities include cardiopulmonary, gastrointestinal and renal, as well as neurobehavioural sequelae.[14] Sound science linking male infertility with cocaine abuse is lacking. Some of the specific effects have been best understood through animal studies.

Cocaine stimulates the central and peripheral nervous systems, affecting behaviour and mood. Men with a history of prolonged cocaine use claim to have decreased libido, and erectile and ejaculatory dysfunction. Cocaine use has been implicated to cause hyperprolactinaemia and hypotestosteronaemia, which in turn inhibit spermatogenesis. These effects are dose and duration dependent, with studies showing that cocaine use for more than five years is associated with abnormalities of sperm concentration, motility and morphology.[3,14]

Amphetamines and ecstasy

The impact of amphetamines and ecstasy (3,4-methylenedioxy-N-methylamphetamine) on sperm quality and function has been studied through rat models. Amphetamines cause a dose-dependent reduction of plasma testosterone and DNA damage at higher levels. Ecstasy causes a similar effect but is associated with higher levels of DNA damage, tubular degeneration and interstitial oedema. Asthenospermia and teratozoospermia are not seen.[13]

Opioid narcotics

Methadone and heroin

Methadone and heroin are both opiates that cause sedation and decreased pain perception by their depressant action on the central nervous system. Studies conducted more than three decades ago indicated that methadone maintenance tends to suppress male sexual function more significantly than heroin use. This may be a result of either the higher potency of methadone or its slower clearance from the body. Both methadone and heroin have been shown to cause lower serum testosterone concentrations, affect sperm motility and cause lower ejaculate volumes secondary to their alpha-adrenergic blocking properties. Abnormal sexual dysfunction seems to continue even after cessation of use.[3,13]

Prescription opiates

Men who are on long-term morphine (oral, transdermal or intrathecal) have lower LH and testosterone levels, a higher incidence of erectile dysfunction and decreased libido. There is conflicting evidence as to whether the levels of LH and testosterone differ when different narcotic drugs are used.[13] Androgen supplements may help improve sexual function in such patients, but it must be borne in mind that such supplements will also inhibit sperm production.

Anabolic androgen steroids

The abuse of anabolic androgen steroids (AAS) by amateur and professional athletes to enhance performance is well established. Steroids are also reported to be found in 'dietary supplements', which are claimed to be AAS-free. International surveys recently reported an overall steroid contamination rate of 15–25 per cent, depending on the country.[15]

Anabolic androgen steroids include not only testosterone, but also its synthetic derivatives, where structural changes have been made to maximise its anabolic and reduce its androgenic effects. The anabolic effects, which include growth promotion as well as protein and collagen synthesis, are usually found at supraphysiological levels of testosterone (>1000ng/dl). These concentrations can be achieved with weekly doses of 300mg or above.

Anabolic androgen steroids induce a state of hypogonadotrophic hypogonadism causing reduced testosterone concentrations. Abusers may present with testicular atrophy, impaired spermatogenesis with oligoasthenoteratozoospermia or azoospermia. Though serum androgens may be supraphysiologically high during AAS use, spermatogenesis is suppressed

Lifestyle choice	Suggested effects on male reproductive system	Study models	Evidence of impact on male fertility	Reversibility of effects on cessation/treatment
Smoking	(–) LH, testosterone (–) Spermatogenesis Reduces sperm concentration, motility and morphology Sperm DNA damage	Animal and human studies	Evidence weak from a recent case-control study; most reviews suggest negative trends Negative effects more likely with heavy smoking (>20 cigarettes/day)	Studies in mice suggest sperm parameters could be ameliorated with smoking cessation
Alcohol	(–) FSH and LH Hypotestosteronaemia Primary testicular failure Decreased libido Erectile dysfunction Irritative prostatitis	Animal and human studies	Evidence weak from a recent case-control study; most reviews suggest negative trends Most of the detrimental effects are result of heavy chronic abuse Outcomes of assisted reproductive techniques may be compromised	Mouse model: partial reversal of sperm parameters on cessation Human case report showing complete recovery of sperm parameters from azoospermia within 3 months of cessation
Anabolic steroids	(–) FSH and LH Lower intratesticular testosterone Impaired spermatogenesis Induce germ cell apoptosis	Human	Evidence strong regarding negative effects from available reviews	Complete recovery may be achieved within 4–6 months after cessation hCG and hMG can help recover sperm testicular function when conservative methods fail Higher frequency of XY disomy and disomies between chromosomes 1 and 9 noted, even after recovery
Recreational drugs Marijuana Heroin Methadone Cocaine Amphetamines Opioids	(–) LH, FSH, testosterone Erectile and ejaculatory dysfunction, low libido Sperm DNA damage Asthenospermia in marijuana users	Animal studies*	Evidence weak due to lack of studies; effects likely to be dose and chronicity dependent	Abnormal sexual function may continue after heroin/methadone cessation
*Lack of prospective human studies due to ethical issues.				

Table 1. Effects of substance misuse on male fertility

due to low testicular androgens secondary to the hypogonadotrophic state. Animal experiments have also reported a higher rate of germ cell apoptosis with AAS abuse.

The treatment of the AAS-induced insult can be either conservative or active. Spontaneous recovery has been reported after cessation of AAS use within a relatively short period (four to six months), with three-quarters of the cases even going on to achieve a pregnancy. Experiments in animal models have suggested that AAS abuse mainly alters the Leydig cell population in the testicles. Though these cells regain proliferation after AAS discontinuation, their numbers usually remain lower than average, even after a long duration of AAS cessation.

Active treatment includes the use of human chorionic gonadotrophin (hCG; an LH surrogate) alone or in combination with human menopausal gonadotrophin (hMG; a urinary extract containing FSH and LH). In a study performed on power athletes, it was found that although spermatogenesis could be restored with hCG, sperm morphology and motility continued to be abnormal. Moretti *et al.*[16] used fluorescent *in-situ* hybridisation for sperm chromosomal analysis after spermatogenesis recovery. A higher frequency of XY disomy and disomies between chromosomes 1 and 9 was identified. There have been a few case reports where azoospermia that was persistent, even after prolonged discontinuation of AAS, was reversed after a three- to four-month treatment with hCG. Successful pregnancy has also been reported in these cases.[15,17]

Men should be warned about the implications of AAS use on spermatogenesis and the uncertainty of recovery even after cessation and treatment.

Legal highs/designer drugs

Legal highs are substances used like illegal drugs, but not covered by the current misuse drug laws, and hence legal to possess or use. Examples are mephedrone (meow meow), naphyrone, benzo fury, gamma butyrolactone and synthetic cannabinoids. There has not yet been any literature about the effects of these on reproductive health, but reports have suggested that they carry serious (cardiovascular) health risks.

CONCLUSION

Substance misuse is prevalent in our society and often during the reproductive years of life. Though it has been difficult to establish definitive links to fertility, research has shown negative trends in semen parameters and fertility outcomes (Table 1). Evidence regarding whether these effects are reversible on withdrawal is conflicting. Recent studies suggest that there is poor evidence to support some lifestyle choices, including smoking, alcohol and street drugs, being closely associated with reduced male fertility. Men should be encouraged to cease the use of such substances as general good health advice.

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REFERENCES

1. NICE. *Fertility: assessment and treatment for people with fertility problems.* Clinical guideline 156, February 2013.
2. Practice Committee of the American Society of Reproductive Medicine. Smoking and infertility: a committee opinion. *Fertil Steril* 2012;98:1400.
3. Sharma R, Biedenharn K, Fedor J, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. *Reprod Biol Endocrinol* 2013;11:664.
4. Joo K, Kwon Y, Myung S, Kim T. The effects of smoking and alcohol intake on sperm quality: light and transmission electron microscopy findings. *J Int Med Res* 2012;40:2327–55.
5. Axelsson J, Rylander L, Rignell-Hydbom A, *et al.* The impact of paternal and maternal smoking on semen quality of adolescent men. *PLoS One* 2013;8:e66766.
6. Waylen AL, Metwally M, Jones GL, *et al.* Effects of cigarette smoking upon clinical outcomes of assisted reproduction: a meta-analysis. *Hum Reprod Update* 2009;15:31–44.
7. El-Melegy NT, Ali M-EM. Apoptotic markers in semen of infertile men: association with cigarette smoking. *Clin Urol* 2011;37:495–506.
8. Pvey AC, Clyma JA, McNamee R, *et al.* Modifiable and non-modifiable risk factors for poor semen quality: a case referent study. *Hum Reprod* 2012;27: 2799–806.
9. Vignera S, Condorelli R, Balercia G, *et al.* Does alcohol have any effect on male reproductive function? A review of literature. *Asian J Androl* 2013;15:221–5.
10. Sermondade N, Elloumi H, Berthaut I, *et al.* Progressive alcohol-induced sperm alterations leading to spermatogenic arrest, which was reversed after alcohol withdrawal. *Reprod Biomed Online* 2010;20:324–7.
11. Klonoff-Cohen H, Lam-Kruglick P, Gonzalez C. Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. *Fertil Steril* 2003;79:330–9.
12. Klonoff-Cohen H. Female and male lifestyle habits and IVF: what is known and unknown. *Hum Reprod Update* 2005; 11:180–204.
13. Fronczak CM, Kim ED, Barqawi AB. The insults of illicit drug use on male fertility. *J Androl* 2012;33:515–28.
14. Rizk B, Atterbury JL, Groome LJ. Reproductive risks of cocaine. *Hum Reprod Update* 1996;2:43–55.
15. Parr MK, Flenker U, Schänzer W. Sports-related issues and biochemistry of natural and synthetic anabolic substances. *Endocrinol Metab Clin North Am* 2010; 39:45–57.
16. Moretti E, Collodel G, La Marca A, *et al.* Structural sperm and aneuploidies studies in a case of spermatogenesis recovery after the use of androgenic anabolic steroids. *J Assist Reprod Genet* 2007;24:195–8.
17. de Souza GL, Hallak J. Anabolic steroids and male infertility: a comprehensive review. *BJU Int* 2011;108:1860–5.