Received: 21 September 2021 | Revised: 3 May 2022 | Accepted: 4 May 2022

DOI: 10.1111/andr.13196

ANDROLOGY

WILEY

REVIEW ARTICLE

Addiction and human male fertility: A systematic review and a critical appraisal

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Abstract

Background: Addiction is a global problem that has many negative consequences on human health as well as the quality of life.

Objectives: This review aimed to assess the effect of addiction on human male fertility.

Methods: A systematic review was conducted on various electronic sites.

Results: The initial literature search identified a total of 5239 articles in all searched databases. After removing duplicates and application of inclusion/exclusion criteria, 177 were potential articles, 112 were omitted because no direct relevance was encountered. Finally, 65 studies were retained for review. They were classified according to the type of addiction into; opioids and cannabinoids (18 articles), alcohol (7 articles), cocaine (2 articles), Androgenic Anabolic steroids (AAS, 15 articles), tobacco (10 articles) and caffeine (13 articles). Most of these recruited articles demonstrated a negative impact of the addressed substance on male fertility with variable levels of evidence.

Conclusions: It was concluded that addiction harms human male fertility that should be put into consideration. More future studies are needed after a proper methodological and statistical approach, including logistic regression analysis, to predict the effect of a specific substance on human male fertility.

KEYWORDS
Addiction, fertility, hormones, infertility, semen, substance use disorders

1 | INTRODUCTION

Definition of addiction: Addiction is a worldwide problem that showed a significantly rising prevalence rate, where it could have a deleterious impact on human mental, behavioral, and physiologic health.[1,2] Addiction was formerly defined as the loss of control over drug use, or the compulsive seeking and taking of drugs despite adverse consequences.[3] Substance addiction (or drug addiction) is a neuropsychiatric disorder characterized by a recurring desire to continue taking the drug despite harmful consequences.[4,5] This drug-seeking behavior is associated with craving and generally a loss of control.[6]

Consequently, addiction is caused by the actions of drug abuse and generally requires repeated drug exposure influenced by the genetic makeup of the person and the psychological/social context in which drug use occurs.[7] However, the establishment of a clear definition of addiction has taken great effort over decades, until the American Psychiatric Association established a widely used evidence-based definition with strict criteria for "substance use disorders" in the Diagnostic and Statistical Manual, 5th edition "DSM-V" (American Psychiatric Association, 2013).[8]

Eleven criteria were present in the DSM-V, and the person needs to meet at least 2 of them to be diagnosed as having a substance-use disorder where the severity of the addiction is determined by the number

of criteria met. In general, 2 to 3 symptoms indicate a mild substance use disorder, 4 to 5 symptoms would be called a moderate substance use disorder. If six or more symptoms are present, this would be classified as a severe substance use disorder and is also known as having an addiction (DSM-V criteria).[8]

Despite the above-mentioned achievement in terms of the definition of addiction, the need to cover the relatively new widespread behavioral disorders that may have addictive criteria, such as internet addiction, sex addiction, food addiction, mobile phone addiction, etc. added a wider concept of addiction which is "non-substance use disorders" to the traditional concept of drug or substance use disorders.[9,10]

1.1 | Male fertility and infertility

Based on the latest international glossary on infertility and fertility care, infertility is defined as the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse due to an impairment of a person's capacity to reproduce, either as an individual or with his/her partner. Regular sexual intercourse is an important determinant for the occurrence of pregnancy.[11] The prevalence of infertility in reproductive-aged women has been estimated to be one in every seven couples in the Western world and one in every four couples in the developing countries. In some regions of the world, including South Asia, some countries of sub-Saharan Africa, the Middle East and North Africa, Central and Eastern Europe, and Central Asia infertility rates may reach 30%.[12] Males are found to be solely responsible for 20%–30% of infertility cases but contribute to 50% of cases overall. In their study, Agarwal et al.[13] showed that male infertility rates were highest in Africa and Central/Eastern Europe, whereas corresponding rates for North America, Australia, and Central and Eastern Europe varied from 4.5%–6%, 9%, and 8%–12%, respectively.

Over decades, many causes of human male infertility were extensively studied. However, while the majority of reports focused on the relatively common causes of male infertility such as chromosomal and genetic anomalies, varicocele, endocrinal disrupters, genital tract obstruction, etc. However, a relative scarcity of studies that addressed other contributing factors like environmental and behavioral ones, including addiction, was remarkable. Many articles were conducted on laboratory animals; others were conducted on humans. Also, the primary end point of many articles were measurement of the change that may affect male fertility like testicular volume measurement,[14] changes in reactive oxygen species (ROS) concentrations,[15] etc., while others focused on the direct effect of investigated risk factors on semen parameters or hormonal profile

1.2 | Aim of the work

This systematic review aimed to address the possible consequences of different types of substance addiction on human male fertility.

2 | METHODS

This review followed the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines and used a guided approach to retrieve relevant articles.[16] The population, intervention, comparison, outcome, and study model was used to develop the inclusion criteria and search terms.[17]

2.1 | Literature search

A systematic review was conducted until the end of May 2021 based on a search of all relevant articles in many electronic sites such as: PubMed, Medline Medical Subject Heading, Science Direct, Scopus, Cochrane Library, EMBASE, CINAHL, Academic Search Complete, Google scholar, and Egyptian Knowledge Bank (EKB) databases. Keywords that were used to assess the outcome and estimates for relevant associations were: addiction, substance use disorders, infertility, fertility, semen, hormones.

2.2 | Selection criteria and data extraction

Inclusion criteria were: (a) randomized-controlled trials, case–control studies, cross-sectional studies, cohort studies, and case-series; (b) studies in humans; (c) articles published only in the English language. Exclusion criteria were: (a) irrelevant published or accepted studies, (b) repeated publications, (c) single case reports, (d) editorials, (e) letters to the editor or comments, and (f) review articles. Additionally, the level of evidence of the different studies was assessed according to guidelines of Centre for Evidence-Based Medicine, https://www.cebm.net/

2.3 | Primary endpoint

Recruited studies were considered to have direct relevance to human male fertility and then subjected for review, if their primary endpoint was the changes in the human male hormonal profile or semen parameters in response to substance addiction.

3 | RESULTS

The initial literature search identified a total of 5239 articles in all databases. After application of the above-mentioned inclusion/exclusion criteria, 174 potential articles were recruited. No direct scientific relevance was detected in the additional 112 articles that were omitted and 65 studies were finally retained for review. Further, these articles were classified according to the type of addiction into; opioids and cannabinoids: total of 18 articles (1 for tramadol, 11 for cannabis and/or Marijuana, 1 for Teriak and Shireh and 5 for Heroin), alcohol (7 articles), cocaine (2 articles), Androgenic Anabolic Steroids "AAS" (15 articles), tobacco (10 articles), and caffeine (13 articles). The

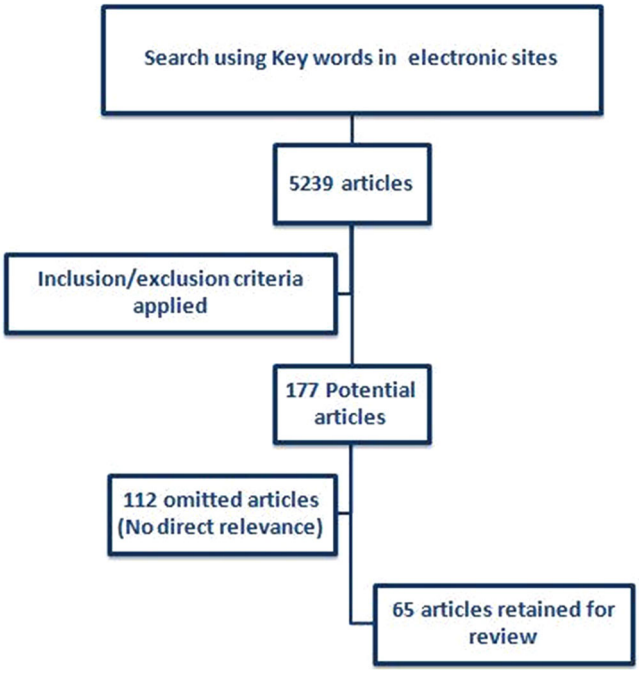

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA). Flowchart of the literature search and selection

flowchart is presented in Figure 1. The total number of the investigated cases was 14,695 compared with 23,828 controls. Besides, these articles were addressed in terms of country, type of the study, type of addiction, number of cases and control, fertility-related confounding factors, main finding, and level of evidence. This is presented in Table 1.

4 | OPIOIDS AND CANNABINOIDS

Many addictive drugs fall into this category that was addressed for their impact on male fertility, including tramadol, Marijuana/cannabis, Teriak and Shireh, and heroin.

4.1 | Tramadol

Tramadol addiction represents a real problem in many countries because of its wide use as a potent opioid analgesic for severe pain control and also for other indications, including treatment of premature ejaculation.[18,19] Although tramadol is generally a scheduled drug, this wide spread consumption for such purposes carry the risk of its increased addition.[20,21] The effect of tramadol on human male fertility was lately addressed in a case-controlled study conducted on 60 Egyptian patients with tramadol abuse (according to DSM-V) compared to 30 healthy control subjects.[22]The authors reported that tramadol abusers had significantly high serum prolactin (PRL), low free testosterone (T) levels, increase percentage of abnormal form, and reduced sperm motility compared to control. (Level of evidence: 3b).

Although no other studies on human subjects were found to support-or contradict- these findings, many animal studies were carried out. Rats treated with tramadol showed increased spermatogenic, Leydig cells, and Sertoli cells apoptosis and reduced T, follicle stimulating hormone (FSH), and luteinizing hormone (LH) compared to the control group.[23] Also, tramadol- induced addiction in rats was reported to cause reduced sperm motility and count, increased oxidative stress (nitric oxide (NO) and malondialdehyde (MDA), and reduced antioxidant capacity (superoxide dismutase, SOD), hormonal changes (reduced T, FSH, LH, and estradiol,E2) and increased testicular apoptosis (histopathologically, and by RT-PCR with increased Bax gene expression and reduced Bcl2).[24] However, another animal study reported that reduced sperm counts in rats treated with tramadol were not related to oxidative stress but rather to decreased T, FSH, and LH.[25]

From accumulated pieces of evidence, tramadol addiction possibly harms male fertility, although further studies on human subjects are needed.

4.2 | Marijuana (Cannabis)

Marijuana, consisting of dried leaves and flowers from the marijuana plant (*Cannabis sativa*), is smoked to release the psychoactive cannabinoid compound delta-9-tetrahydrocannabinol (THC). It was found that cannabinoid compounds are also naturally synthesized by the human body from fatty acid derivatives, endogenous cannabinoids, or endocannabinoids.[26]Cannabis addiction is widely spread all over the world and one recent study reported that 13% of infertility Canadian patients had given a history of chronic use of cannabis.[27]

Eleven studies were reviewed for the possible associations of cannabis and male fertility. Results were quite heterogeneous; as some studies demonstrated a possible link between cannabis consumption and abnormal semen analysis while others do not. Comparison of recruited articles is shown in Table 1.

Pacey et al. (2014)[28] compared 318 cannabis users to 1652 non-users showing that cannabis use is a risk factor for poor sperm morphology. Gundersen et al. [29] examined 1215 men, median 19 years old detecting that cannabis use was associated with lower sperm concentration and total sperm count . Similarly, Carroll et al. [30] reported that cannabis users were at greater risk of asthenozoospermia and teratozoospermia. On the other hand, Verhaeghe et al.,[31] and Lee et al.,[32] showed insignificant differences and semen paramerters among cannabis users versus non-users and by contrast, Nassan et al.[33] showed that cannabis users among men from infertile couples had significantly higher sperm concentrations.

Activation of the endocannabinoid receptors on sperm by either anandamide or THC has also been reported to reduce sperm motility in a dose-dependent manner and inhibit the capacitation-induced acrosomal reaction[34,35]. However, Schuel et al.[36] found a biphasic effect at different concentrations of anandamide. Sperm was inhibited at higher levels but hyper activated at lower levels of anandamide. Reductions in sperm motility may be due to anandamide- or THC-induced inhibition of sperm mitochondrial activity, which initiates sperm apoptosis.[34,37]

TABLE 1 Comparison of the recruited articles (fertility related confounders, main findings and level of evidence)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Bassiony et al. [20]	Egypt	Case-controlled	Tramadol	60	30	Not addressed	Lower sperm count (53.7 ± 39.6 vs. 70.1 ± 26.9 10^6/ml, $p = 0.007$), sperm motility ($p = 0.01$) and normal sperm morphology (p=0.07) vs. controls-Significant increased mean levels serum PRL (91.3 ± 197.7 vs. 11.1 ± 2.1, $p = 0.04$), reduced free T (10.4 ± 17.3 vs. 10.4 ± 17.3, $p = 0.001$).	3b
Kolodny et al. [39]	USA	Case-controlled	Marijuana	20	20	Addressed	Decreased mean T level in users versus non-users (416 ± 34 vs. 742 ± 29 ng/dl, $p < 0.001$)	3b
Cushman et al.[36]	USA	Case-controlled	Marijuana	25	13	Addressed	No differences in the mean levels of serum FSH (14.3 ± 4.6 vs. 14.4 ± 2.1 mIU/ml, $p = 0.941$), LH (11.1 ± 3.1 vs.11.9 ± 3.3, $p = 0.465$) and *T* (639 ± 270 vs. 633 ± 295, $p = 0.950$) levels in users vs. non-users	3b
Vescovi et al. [40]	Italy	Case-controlled	Marijuana	10	10	Addressed	Reduced mean LH levels in users versus non-users (5.8±1.5 vs. 10.5±1.3 mIU, $p < 0.05$).	3b
Pacey et al. [26]	UK	Cohort	Cannabis	318	1652	Excluded in selection criteria	Increased risk for abnormal forms in cannabis users (OR = 1.94, 95% CI 1.05-3.60) at age < 30 years, (OR = 1.35, 95% CI 0.63–1.29) aged 31–40 years, and (OR = 0.97, 95% CI 0.20–4.76) at age > 40 years.	2b
Gundersen et al. [27]	Denmark	Cohort	Marijuana	554	661	Addressed	- Regular marijuana smoking > once/week was linked to 28% (95% CI: −48, −1) lower sperm concentration and 29% (95% CI: −46, −1) lower total sperm count after adjusted confounders. Combined use of marijuana > once/week and other recreational drugs reduced sperm concentration by 52% (95% CI: −68, −27) and total sperm count by 55% (95% CI: −71, −31) vs. controls. - Increased serum T levels in cannabis users by 7% (95% CI: 0, 14) compared with non-users.	2b
Thistle et al. [37]	USA	Cohort	Marijuana	692	614	Addressed	No difference in serum *T* between ever users (adjusted mean = 3.69 ng/ml 95% CI: 3.46, 3.93) and never users (adjusted mean = 3.70 ng/ml, 95% CI: 3.45, 3.98). Serum *T* was inversely linked to time since last regular use ($p = 0.02$), and serum *T* was inversely linked to time since last use ($p < 0.01$).	2b

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Lizano et al. [38]	USA	Case controlled	Marijuana	10	11	Not addressed	No statistical differences in the mean *T* levels between Marijuana users and non-users (7.13 ± 2.59 vs. 8.49 ± 6.32, $p = 0.65$).	3b
Nassan et al. [31]	USA	Cohort	Marijuana	365	297	Addressed	Men who had ever smoked marijuana had significantly higher sperm concentration (62.7; 95% CI: 56.0, 70.3) 10^6/ml) vs. men never smoked (45.4 (38.6, 53.3) 10^6/ml, p = 0.001). No significant differences in sperm concentration between current (59.5 (47.3, 74.8) 10^6/ml) and past marijuana smokers (63.5 (56.1, 72 10^6/ml; $p = 0.60$).	2b
Carroll et al. [28]	Jamaica	Cross-sectional cohort study	Marijuana	107	122	Addressed	Recent users of large quantities of marijuana were 2.6 times (95% CI, 1.0–6.8, $p = 0.044$) and 4.3 times (95% CI: 1.1–15.9, $p = 0.030$) at greater risk of asthenozoospermia. Moderate quantity users were 3.4 times (95% CI: 1.5–7.9, $p = 0.004$) more likely to be diagnosed with teratozoospermia	4
Verhaeghe et al. [29]	France	Case-controlled	Cannabis	27	27	Addressed	No significant difference in semen or hormone levels. Rates of sperm aneuploidy ($p = 0.004$), diploidy ($p = 0.037$), total chromosome abnormalities ($p = 0.003$) and DNA fragmentation ($p = 0.027$) were significantly higher in cannabis users than in non-cannabis users.	3b
Lee et al. [30]	USA	Cross-sectional	Cannabis	12	–	Not addressed	Serum reproductive hormones were within normal ranges, except PRL that increased in 50% of cases. Cannabinoid metabolite levels in semen and blood are comparable.	4
Safrenijad et al. [49]	Iran	Case-controlled	Opiates	186	188	Excluded in selection criteria	Opiate users had significant decreases of mean sperm concentration (22.2±4.4 vs. 66.3±8.3 10^6/ml, p = 0.002), sperm motility (38.2 ± 7.2 vs. 61.8 ± 5.1%), normal forms (24.8 ± 4.3 vs. 63.7 ± 4.4%, p = 0.001), acrosome reaction percentage (24± 8 vs. 35±11%, $p = 0.02$), and had significant increases in mean fragmented DNA (36.4%±3.8% vs. 27.1%±2.4%, $p = 0.004$) compared to controls	3b
Ragni et al. [51]	Italy	Cross-sectional	Heroin and/or methadone	32	–	Excluded in inclusion criteria	The most frequent abnormality was in sperm motility (78%), followed with teratozoospermia (28%) and oligozoospermia (16%). Patients taking methadone only ($n = 7$) had neither teratozoospermia nor oligozoospermia.	4

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Ragni et al. [52]	Italy	Cross-sectional	Heroin and/or methadone	80	–	Excluded in inclusion criteria	In all cases asthenospermia was one of the abnormalities (100%), 24% showed teratospermia and hypospermia and 17% showed oligozoospermia. Such seminal pathology, especially of forward sperm motility, even in combination with normal hormone levels, might be an early indication of heroin toxicity to the male reproductive tract.	4
Nazmara et al. [53]	Iran	Case-controlled	Heroin	25	25	Excluded in selection criteria	Sperm motility (42.93% ± 3.89% vs. 68.9% ± 2.68%, $p = 0.001$), and sperm viability (73.27%±3.85% vs. 86.48%±1.05%, $p = 0.01$) leucocytes (1.48±0.37 vs. 9.26±1.86, $p = 0.001$), sperm histone replacement abnormalities (32.33% ± 10.89% vs. 5.56%±0.85%, $p = 0.005$) had significant differences in addicted group vs. non-exposed ones. No significant difference in hormonal profile.	3b
Nazmara et al.[54]	Iran	Case-controlled	Heroin	24	24	Excluded in inclusion criteria	Seminal leucocytes (1.69±0.41 vs. 8.61±1.73, $p = 0.001$), sperm motility (65.51±2.57 vs. 41.96±3.58, $p = 0.001$) and survival rate (87.41±1.00 vs. 71.50±4.59, $p = 0.002$) of sperms were significantly different between healthy and addicted groups. The mean levels of protamine-2 gene and protein expression in the addicted group (0.05±0.02 and 0.10±0.02, were significantly lower than healthy group (3.59±0.94 and 0.27±0.06, $p = 0.002$ and $p = 0.017$). Seminal miRNA-122 levels in addicted men were statistically higher than in healthy men (3.51±0.73 vs.1.52±0.54) ($p = 0.034$).	3b
Rezaei-Mojaz et al. [55]	Iran	Case-controlled	Heroin	24	24	Excluded in inclusion criteria	There were significant differences in sperm total motility (41.07 ± 3.63 vs. 63.03% ± 3.31%, $p = 0.001$), progressive motility (35.21% ± 2.64% vs. 20.93% ± 3.22%, $p = 0.001$) and viability (69.9% ± 4.69% vs. 86.81% ± 1.26%, $p = 0.002$) in addicted group vs. controls. Duration of drug dependence was inversely correlated with sperm viability ($p = 0.016$) and sperm motility ($p = 0.05$).	3b
Lindholm et al.[56]	Denmark	Cross-sectional	Alcohol	30	–	Excluded in inclusion criteria	Testicular disorder in chronic alcoholism may be independent of liver disease	4
Sengupta et al. [58]	India	Case-controlled	Alcohol addiction (DSM III	38	24	Not addressed	Significant elevation of serum LH and a trend of low serum T were noted with scant evidence of advanced liver disease. None of the alcoholics had clinical stigmata of hypogonadism and feminization.	3b

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Heinz et al.[59]	Germany	Case-controlled	Alcohol addiction (DSM III-R)	12	14	Not addressed	During withdrawal, LH, estradiol, and cortisol levels were significantly enhanced. Estradiol and cortisol concentrations fell significantly during abstinence, whereas LH concentrations remained elevated.	3b
Gümüş et al.[60]	Turkey	Case-controlled	Alcohol	45	30	Not Addressed	In the absence of hepatic and gonadal failure in chronically alcoholic men, there is no significant difference in serum hormonal levels between alcoholics and healthy non-alcoholic men ($p > 0.05$)	3b
Muthusamiet al.[61]	India	Case-controlled	Alcohol	66	30	Excluded in selection criteria	Alcoholics showed a significant increase in FSH ($p = 0.001$) and LH ($p = 0.001$) E2 ($p = 0.001$) levels whereas PRL ($p = 0.536$) did not show significant change in alcoholics compared to controls. The mean *T* ($p = 0.001$) and progesterone ($p = 0.001$) levels in alcoholics showed significant decreases compared with controls. In alcoholics, sperm count ($p = 0.001$), percentages of progressively motile sperms ($p = 0.001$), and normal sperm morphology ($p = 0.001$) were significantly decreased compared with the controls.	3b
Maneesh et al.[62]	India	Case-controlled	Alcohol	46	55	Excluded in selection criteria	Alcohol abusers had significantly low serum T($p = 0.001$) with low serum LH ($p = 0.7537$) and FSH ($p = 0.989$). Alcohol caused high extent of lipid peroxidation ($p = 0.004$), and increased activities SOD ($p = 0.001$ and GSH-ST ($p = 0.006$). Serum T level in alcoholics is negatively correlated with duration of alcohol abuse ($p = 0.001$)	3b
Jensen et al.[63]	Denmark	Cohort	Alcohol	533	Total population 1221	Addressed	An inverse dose–response association between alcohol intake and sperm concentration ($p = 0.02$), total sperm count ($p = 0.01$) and normal sperm morphology ($p = 0.01$). Sperm concentration and percentage morphologically normal sperms were lower in men with alcohol intake > 40 units compared to men with an intake of 1–5 units weekly 0.39 (95% CI −0.92 to 0.14) and 0.51 (95% CI 1.03 to 0.01). SHBG was reduced with increase of free T level.	2b
Bracken et al. [71]	USA	Cohort	Cocaine	Not clarified	Total population1309	Addressed	Cocaine use was associated with increased risk of low sperm count (OR 2.1, 95% CI: 1.0–4.6). Duration of use was linked to decreased sperm count, motility and normal forms (OR 2.0, 95% CI 1.0–4.1)	2b

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Samplaski et al.[72]	Canada	Cohort	Cocaine	38	4400 infertile men	Addressed	While infrequent cocaine use seems to have limited impact on semen parameters. 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%).	2b
Aakvaag & Stromme[77]	Norway	Randomized placebo-controlled trial	Mesterolone AAS	10	11	Not clarified	No effect on the plasma levels of LH and FSH were detected. After 4 weeks on 75 mg mesterolone/day a significant ($p < 0.01$) drop in the mean value for plasma T level was observed, 5.2 to 4.0 ng/ml. After another 4 weeks on 150 mg mesterolone/day a further decrease to 3.5 ng/ml was found. During mesterolone administration, the protein binding of T in plasma was significantly reduced.	1b
Holma & Adlercreutz,1976[78]	Finland	Cross-sectional	Metandienone (AAS)	16	–	Not clarified	During administration of metandienon the mean plasma T level fell 69%, from 29.4 ± 11.6 nmol/1 to 9.1 ± 7.5 nmol/1. The mean plasma levels of LH and FSH fell significantly ($p < 0.001$ and $p < 0.01$), both about 50%. Maximum stimulation values after LRH administration were lower than pre-treatment values.	4
Holma[79]	Finland	Cross-sectional	Metandienone (AAS)	15	–	Not clarified	-Semen: reduced count, motility and normal forms -Acid phosphatase also decreased&&&&&-Fructose decrease after one month but not after two months	4
Remes et al. [80]	Finland	Randomized placebo controlled, crossover trial	Methandie-none (12) and DHEAS (16) cases)	12 16	12 16	Not clarified	-Methandienone and-DHEAS: significant decrease T-FSH, LH: no significant decrease with both drugs	1b
Schurmeyer et al.[81]	Germany	Case-series	19-nortetsosteroi (AAS)	5	–	Excluded in selection criteria	-Reversible azoospermia in response to 19-nortesosterone injection-Reversible reduced gonadotropin and free T	4

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Ruokonen et al.[82]	Finland	Cross-sectional	AAS	9	–	Not addressed	Self-administration of T and anabolic steroids led to impaired testicular endocrine function characterized by low concentrations of T precursors, high ratios of T to its precursor steroids and low SHBG concentrations. Decreased concentrations of SHBG and testicular steroids were still partly evident during the 16 weeks after drug withdrawal. The depressed circulating levels of dehydroepiandrosterone and its sulfate may indicate that the androgenic–anabolic steroids also suppress adrenal androgen production.	4
Alen et al.[83]	Finland	Case series	Multiple AAS	7	–	Not clarified	-Reversible decrease of FSH, LH long-lasting decrease of *T*	4
Knuth et al., 1989[84]	Germany	Case-controlled	Multiple AAS	41	41	Addressed	-Semen: reduced count, motility and normal forms, reversible-Hormones: low FSH, LH and high E2, reversible	3b
Torres-Calleja et al.[85]	Mexico	Case-controlled	Multiple AAS	15	15	Addressed	- AAS users, eight had sperm counts under the lower normal limit, three had azoospermia, two polyzoospermia, and two had normal sperm counts. Normal forms were significantly reduced&&&&&-Control group, only one subject had oligozoospermia&&&&&-Reduced FSH and PRL in AAS users	3b
Karila et al. [86]	Finland	Cross-sectional	AAS	18	–	Not clarified	The concomitant abuse of HCG and supra-physiological AAS dose cause transient impairment on semen quality in males, although spermatogenesis is maintained with this regimen despite prolonged abuse of massive doses of AAS.	4
Bonetti et al.[87]	Italy	Cross-sectional	Multiple AAS	20	–	Excluded in selection criteria	-Decrease FSH, LH and SHBG-Semen: significant decrease of concentration-Reduced testicular volume in five cases	4

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Al-Janabi et al.[88]	Iraq	Case-controlled	AAS	16	8	Not clarified	The use of AAS resulted in the impairment of spermatogenesis being significantly low in AAS group compared to the controls. Sperm agglutination and round cells increased significantly within AAS group in AAS group compared with the controls. Likewise, serum FSH and LH increased significantly in AAS group, 12 weeks after the cessation of AAS compared to baseline. Although PRL level was within the normal range in AAS group, it was significantly low in AAS group compared to the controls.	3b
Coward et al.[89]	Great Britain	Cohort	AAS		97	Total population 6033 cases	Profound hypogonadism, defined as testosterone 50 ng/dl or less, was identified in 97 men (1.6%) in the large retrospective cohort. The most common etiology was prior anabolic androgenic steroid exposure, which was identified in 42 men (43%).	2b
Windfeld-Mathiasen et al.[90]	Denmark	Case-controlled	ASA	545	5450	Not addressed	Androgen use was associated with a temporary decline in fertility and most androgen users achieved parenthood without any help from the health care system. Overall, the fertility rate and the prevalence of assisted reproduction among androgen users were close to those in the background population.	3b
Rasmussen et al.[91]	Denmark	Cross-sectional	ASA	88	44	Addressed	Serum INSL3 is reduced years following AAS cessation in men, independently of testosterone, suggesting persistently impaired Leydig cell capacity.	4
Dikshit et al.[107]	India	Case-controlled	Tobacco	119 chewers 219 smokers	288	Excluded in selection criteria	No significant differences is semen parameters recorded	3b
Chia et al.[108]	Singapore	Case-controlled	Tobacco	137	472	Excluded in selection criteria	Smoking produce dose dependent reduction of sperm count increase of abnormal forms especially the head	3b

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Merino et al.[109]	Mexico	Case-controlled	Tobacco	197	161	Not addressed	Smokers had significantly poorer sperm density, a lower percentage of viability, a lower percentage of normal sperm morphology and the percentage of motile sperm was lower ($p < .005$). These parameters were worse in the heavy smoking groups.	3b
Said et al.[110]	India	Cross-sectional	Tobacco	638 chewers (mild-moderate severe)	–	Not addressed	Sperm concentration, percentage motility, morphology, and percentage viability were significantly higher in the mild group vs. the moderate group and in the moderate group vs. the severe group	4
Pasqualotto et al.[111]	Brazil	Cohort	Tobacco	Mild 143, moder-ate154, heavy 70	522	Not addressed	There were no significant differences among the groups in sperm concentration or motility, or in levels of FSH,LH, or serum total T.	2b
Davar et al.[112]	Iran	Case-controlled	Tobacco	98	53	Not addressed	No significant difference in semen parameters recorded	3b
Blanco-Muñoz et al.[113]	Mexico	Case-controlled	Tobacco	-40 ex-smokers-67 current smokers	29	Addressed	Current smokers ≥ 5 cigarettes/day showed significantly higher levels of LH, prolactin and testosterone. Current smokers < 5 cigarettes/day also showed higher levels of prolactin and testosterone. Hormone levels of ex-smokers were similar to those of never-smokers.	3b
Asare-Anane et al.[114]	Ghana	Case-controlled	Tobacco	95	45	Excluded in selection criteria	Smokers were at a higher risk of developing oligospermia, asthenozoospermia and teratozoospermia (OR = 3.1, 4.2 and, 4.7)	3b
Mostafa et al.[115]	Egypt	Case-controlled	Tobacco	50	45	Not addressed	A significant decrease has been shown in sperm count, progressive motility, percentage of normal forms and viability between infertile nonsmoker and infertile smokers.&&&&&The percentage of abnormal sperm chromatin condensation was significantly higher in smokers compared to nonsmokers. A linear correlation was detected between the extent of cigarette smoking and the degree of worsening in progressive motility, total motility, viability and normal morphology .	3b

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Shah et al.[116]	Pakistan	Case-controlled	Tobacco	60	60	Excluded in selection criteria	Total testosterone was found to be significantly high in smokers and smokeless tobacco users, while the level of kisspeptin was found to be significantly high in smokeless tobacco users only as compared to control group	3b
Marshburn et al. [121]	USA	Case-controlled	Caffeine	280	166	Excluded in selection criteria	Drinking 4 cups or more of coffee/day diminishes sperm motility and increases the percentage of dead sperms.	3b
Oldereid et al. [122]	Norway	Case-controlled	Caffeine	193	45	Not clarified	No relationship could be established between sperm concentration, motility and morphology, and the number of cups of coffee drank daily	3b
Prazzini et al.[123]	Italy	Case-controlled	Caffeine	97	121	Age, education, smoking, Alcohol were addressed -Other factors not addressed	Adjusted rate ratios for dyspermia were significantly higher in men drinking 2–3 and ≥4 cups/day (reference 0–1), compared either to normospermic men (1.8 and 3.0 respectively) or men of unknown semen quality (RR 1.3 and 4.2 respectively).	3b
Vine et al.[124]	USA	Cross-sectional	Caffeine	100	–	Age, smoking, and alcohol addressed- Other factors not addressed	No convincing evidence was found for associations between the means, standard deviations, or skewness of any of nine sperm nuclear morphometric parameters and caffeine exposure	4
Klonoff-Cohen et al.[64]	USA	Cross-sectional	Caffeine	221	–	Smoking, alcohol, education, partner's age, race, ART indication, number of attempt were addressed- Other factors not Addressed	Male caffeine consumption had no relation with semen parameters, clinical pregnancy or achieving a live birth.	4

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Sobreiro et al.[125]	Brazil	Cross-sectional	Caffeine	500	–	Not addressed	Among patients not drinking coffee, progressive motility averaged 57.1%, whereas for the patients who consumed more than six cups of coffee/day, it averaged 62.4%. There were no significant differences in semen volume, sperm concentration or sperm morphology recorded	4
Kobeissi et al.[126]	USA	Case-controlled	Caffeine	120	100	Family history of infertility, reproductive health index, smoking, soft drinks intake, occupational exposures were addressed -Other Factors not addressed	-Cases had a slightly higher mean intake of coffee (cups/day 3.2 ± 4.7 vs. 2.9 ± 4.7, $p = 0.574$). -OR of caffeine intake for being infertile were 1.05.	3b
Ramlau-Hansen et al.[127]	Denmark	Cross-sectional	Caffeine	343	–	abstinence time, disorders of reproductive organs, smoking, season,	Caffeine exposure did not seem to affect adversely the semen quality or the levels of serum inhibin B or FSH. No association between caffeine and sperm motility or morphology. Men with a high caffeine intake had about 14% higher concentration of serum T than men with a low caffeine intake.	4
Jensen et al.[128]	Denmark	Cohort	Caffeine Cola	1241 2014	1164 379	Excluded by stepwise regression analysis	Only high cola intake was associated with low sperm concentration	2b
Wogatzky et al. [129]	Austria	Cohort	Caffeine	Caffeine consumers 1321	Total population 1683 cases undergoing ART	Excluded in inclusion criteria	Although single parameters had minor effects on sperm parameter, the combination of age, BMI, coffee intake, ejaculatory frequency and duration of sexual abstinence were identified as factors having a negative effect on sperm motility. Additionally, MSOME (Motile Sperm Organelle Morphology Examination) quality was reduced. The negative impact of age, BMI and coffee intake on sperm quality could be compensated if patients had a high ejaculation frequency and shorter periods of sexual abstinence. 204 men out of 1321 drinking coffee had an intake of more than 3 cups of coffee per day. These patients revealed a marked tendency toward lower sperm quality.	2b

(Continues)

TABLE 1 (Continued)

Reference	Country	Type of Study	Studied substance	No of cases	No of controls	Infertility related Confound variables	Main finding	Level of evidence
Belloc et al.[130]	France	Cohort	Caffeine	Not clarified	Total population 4474	Not clarified	Caffeine consumer were reported to have significant high volume and low sperm concentration compared to non-consumers	4
Yang et al. [131]	China	Case-controlled	Caffeine	189	605	Age, tobacco and alcohol consumption, duration of abstinence, BMI, coffee/cola/fried food/baked foods users were addressed -Other factors not Addressed	Coffee consumption was found to be associated with increased progressive and non-progressive sperm motility of 8.9% or 15.4% for men consuming 1–2 cups/week or 3 cups/week of coffee, respectively. Cola consumption was associated with decreased semen volume at 4.1% or 12.5% for 1–2 bottles/week or 3 bottles/week.	3b
Radwan et al. [132]	Poland	Cross-sectional	Caffeine	286	–	age, smoking, alcohol, diseases, BMI, duration of infertility, abstinence, stress level, cell phone use was addressed -Other factors not addressed	Coffee drinking were not related with any of the examined parameters of sperm DNA damage and high DNA stainability	4

The literature is similarly discordant regarding the effect of cannabis use on total T or pituitary gonadotropin hormones levels. Four studies suggested that there is no difference in T or gonadotropin levels between cannabis users and non-users.[31,38–40] However, one study suggested that cannabis users had higher T levels[29] in contrast to the early report decreased total T levels in subjects using cannabis by Kolodny et al. [41] A reduced FSH was reported by Nassan et al.[33] and a reduced LH was reported by Vescovi et al.[42]

Several limitations warrant mention. First, cannabis use profiles were not reported in most of studies which limit the interpretability of the results as the differences in frequency and quantity of cannabis use are common.[43] Such variability in the profiles of cannabis use also prevented the examination of a dose-dependent effect of cannabis use. Furthermore, recruitment of cases may lead to bias, either related to age or recruitment location. Finally, all studies utilized self-reported cannabis use which may be not reliable because of the social stigma or fear of repercussions.

Many studies tried to explore the possible mechanism by which cannabis could affect male fertility. Cannabis contains more than 460 known products, including more than 60 cannabinoids. Among these cannabinoids, the most active compound is Δ9-tetrahydrocannabinol (Δ9-THC) that exerts its action on the cannabinoid receptors. Two types of cannabinoid receptors are recognized, type 1 (CBR1) and type 2 (CBR2).[44,45] Both CBR1 and CBR2 have an endogenous ligand (anandamide).[26] The endo-cannabinoids has been identified at different levels of the male reproductive tract, and this system was suggested to play a physiological role in both the endocrine and exocrine testicular functions and consequently, in male fertility.[46–48] Only lately, Hazem et al.[49] reported that mature sperms from 50 fertile and 50 infertile groups showed significantly higher levels of both CBR 1 and 2 mRNA expression compared to the immature sperms being significantly more important in the fertile group. In mature sperms, CBR1 expression was significantly related to variation in sperm morphology, and CBR2 was significantly related to both sperm morphology and linearity index. The authors concluded that CBR1 and CBR2 mRNA expression can closely direct sperm maturation at different steps of the reproductive process. It is then possible that cannabis addiction reduces male fertility through its metabolite (Δ9-THC) that competes with ECS for CBR1 and CBR2disrupting this physiologic homeostasis.

From the accumulated pieces of evidence according to the results of the above-mentioned studies, the most consistent effect of cannabis addiction was its negative impact on the sperm morphology while its impact on other semen parameters and hormonal profile is still questionable.

4.3 | Teriak and Shireh

Opium use in Iran commonly consists of Teriak (crude opium), Shireh (a refined opium extract), and Sukhteh (opium dross left in pipes after smoking opium). Teriak and Shireh can be smoked or ingested.[50] In a case-controlled study, Safarenijad et al. [51] investigated 186 Iranian addicts to these two opiate derivatives (addiction was defined according to DSM-IV-RT) against 188 healthy control subjects. Participants were tested for semen analysis, antioxidant capacity (SOD and catalase-like activity), and sperm DNA damage (sperm chromatin structure assay). Significant reduction in sperm count, motility, and normal form, together with reduced antioxidant capacity and acrosome activity was recorded in the addict's group. An increase in DNA fragmentation was also recorded in the addict's group compared to the controls (level of evidence: 3b). The authors concluded that addiction to these substances has a significant adverse effect on semen quality and recommended inquiry of cases of unexplained infertility for possible abuse of these substances. Accordingly, Teriak and Shireh possibly hurt male fertility, but no other studies are available to support or contradict this finding.

4.4 | Heroin

Heroin is an opioid drug made from morphine, a natural substance taken from the seed pod of the various opium poppy plants grown in Southeast and Southwest Asia, Mexico, and Colombia. Heroin can be a white or brown powder, or a black sticky substance is known as black tar heroin.[52] Heroin addiction, an inhalant opioid, was investigated for its impact on male fertility in few studies. Ragni et al.[53] studied 32 heroin and methadone addicts, divided into four groups according to the type of drugs used: 5 heroin-dependent, 10 taking methadone plus heroin more or less constantly, 10 taking methadone plus heroin occasionally, and 7 taking methadone only. Ninety-three percent of the heroin addicts and 65% of those taking methadone had abnormal semen. The most frequent abnormality was in sperm motility (78%), then teratozoospermia (28%), and oligozoospermia (16%). The seven patients taking methadone only had neither teratozoospermia nor oligozoospermia.

Ragni et al.[54] pointed out that the gonadal function was elevated in 80 male heroin and/or methadone addicts by measuring basal plasma levels of FSH, LH, PRL, and T. In 41 subjects, semen analyses were also undertaken. Three groups were distinguished consisting of 15 heroin addicts, 42 undergoing methadone treatment but continuing to take heroin, and 23 taking only methadone. All patients had normal plasma levels of FSH, LH, and T. PRL levels were normal in all subjects except for the 15 heroin addicts, in whom they were significantly higher than in controls. Semen analyses from all of the heroin addicts and the dual heroin–methadone users were abnormal, whereas only 10/22 (45%) of the methadone takers were pathological. In all cases, asthenospermia was one of the abnormalities (100%), 24% also showed teratospermia and hypospermia and 17% showed oligozoospermia. Such seminal pathology, especially of forward sperm motility, even in combination with normal hormone levels, might be an early indication of heroin toxicity to the male reproductive tract.

In their study, Nazmara et al. [55] investigated 25 heroin addicts for at least 1 year before enrollment compared to 25 non-exposed healthy men. The participants were investigated for semen profile, hormonal levels, and sperm nuclear histone to protamine ratio. These authors reported significantly lower sperm motility, sperm normal forms, and

viability and significantly higher white blood cells in addicts versus the healthy control group. No significant difference in hormonal profile was recorded. A significantly higher histone replacement anomaly was recorded in addicts compared to the non-exposed group (level of evidence: 3b).

Later, Nazmara et al. (2020)[56] investigated 24 fertile men without any and 24 addicted men who used only heroin for at least 4 months. Among the studied variables, body mass index, seminal pH, white blood cells count in the semen, motility was significantly different between the healthy and addicted groups. Besides, the levels of protamine-2 gene and protein expression in the addicted group were significantly lower than in the healthy group. Seminal miRNA-122 levels in addicted men were higher than in healthy men. These researchers concluded that heroin abuse may lead to male infertility by causing leukocytospermia, asthenozoospermia, protamine deficiency, and seminal plasma miRNA profile alteration.

Rezaei-Mojaz et al.[57] estimated 2enkephalin-degrading enzymes, aminopeptidase N (APN/ CD13), and endopeptidase (NEP/CD10), gene and protein expression levels in sperm samples of fertile and heroin-addicted men. There were significant differences in sperm total motility, progressive motility, and viability in the addicted group versus controls. APN and NEP gene expression levels in the addicted group were decreased compared with the controls. The average percent of APN/CD13 in heroin consumers significantly decreased compared with the healthy ones, while NEP/CD10 rate between the two groups was similar. The duration of drug dependence was correlated with sperm viability and motility, NEP, and APN gene expression levels. It was concluded that semen quality and enkephalin-degrading enzymes were altered in heroin-addicted men.

Accordingly, heroin addiction has a possible negative impact on male fertility although further studies still needed.

4.5 | Alcohol

Alcohol addiction is the oldest type of addiction in humans, dating thousands of years ago. Previously, Lindholm et al.[58] assessed the testis and liver histology, and pituitary-testicular function in 30 chronic alcoholics. Severe reduction of spermatogenesis was found in 30% and in these patients, serum FSH and PRL concentrations were significantly higher. There was no correlation between abnormalities in the liver and testis. Serum T was normal in most cases. Sexual dysfunction and testicular atrophy occurred in more than half of the patients and were not related to liver disease. It was concluded that the testicular disorder in chronic alcoholism may be independent of liver disease.

Rallo et al.[59] investigated 11 male chronic alcoholics without cirrhosis compared to 10 healthy controls. Basal levels of FSH, LH, and E2 were higher and the T level lower in the alcoholic group.

Sengupta et al.[60] assessed the serum levels of LH, T, and hepatic functions were measured in 38 male alcoholics and 24 male control subjects. Significant elevation of serum LH and a trend of low serum T were noted with scant evidence of advanced liver disease. None of the alcoholics had clinical stigmata of hypogonadism and feminization.

Heinz et al.[61] estimated serum LH, FSH, T, androstenedione, estradiol, sex hormone-binding globulin, cortisol, and PRL in 12 male chronic alcoholics once during withdrawal and once after 21 days of abstinence compared to those of 14 healthy volunteers. During withdrawal, LH, estradiol, and cortisol levels were significantly enhanced. Estradiol and cortisol concentrations fell significantly during abstinence, whereas LH concentrations remained elevated. It was suggested that the well-known inhibitory effect of alcohol on the biosynthesis of T may have led to a compensatory increase in LH secretion so that normal serum concentrations of T were maintained. On the other hand, peripheral conversion from androstenedione to estradiol via aromatase pathways seemed to be enhanced in chronic alcoholics, at least during withdrawal.

In their study, Gümüş et al.[62] assessed the effect of chronic alcoholism on serum hormone levels. No significant difference in hormone levels between groups was found except for serum FSH. It was concluded that in the absence of hepatic and gonadal failure in chronically alcoholic men, there is no significant difference in serum hormonal levels between alcoholics and normal healthy non-alcoholic men.

Additionally, Muthusami et al.[63] investigated 66 Indians alcoholic addicts (drinking a minimum of 180 ml alcohol/day 5 times/week for at least 1 year) against 30 non-alcoholics. These authors reported a significantly low semen volume, sperm concentration, sperm motility, and sperm normal forms in alcohol compared to the healthy controls. They also reported significantly low T, and high FSH, LH, E2 levels in the same group compared to the control. (Level of evidence: 3b).

In another study conducted by Maneesh et al.,[64] 46 Indian male alcohol abusers in the age group 20–40 years were investigated for their hormonal profile and oxidative stress against 55 men of matched age. Alcohol abusers had significantly low plasma T with low LH and FSH. Besides, they had significantly high thiobarbituric acid reactive substances (TBARS), superoxide dismutase and glutathione S-transferase, and low glutathione, ascorbic acid, catalase, glutathione reductase, and glutathione peroxidase. The serum T level in alcoholics was negatively correlated with the duration of alcohol abuse, and TBARS. It was concluded that there was a duration-dependent decreased serum T level in alcohol abusers that could be attributed to increased oxidative stress which can damage Leydig and supporting Sertoli cells and/or through the impaired HPG axis. Despite the fact this study addressed the hormone profile changes in alcoholism, reports of the semen profile of the participants were not available to point out the direct effect of these changes on the participant's fertilizing capacity. (Level of evidence: 3b).

Inline, Jensen et al.[65] studied the effect of habitual alcohol intake in (533 among a total of 1221 Danish men on the seminal parameters and sex hormone level. Sperm concentration, sperm motility, and sperm normal forms were negatively associated with habitual alcohol intake, while SHBG was reduced with subsequent increase of free T level. (Level of evidence: 2b).

Apart from the above-mentioned studies, no other studies addressed the direct effect of alcoholism on male fertility determinants, like semen parameters, although plenty of articles were found

to address the impact of alcoholism on female fertility and the outcome of assisted reproductive techniques.[66–69]

The mechanism of impaired male fertility due to alcoholism is probably related to its effect on the hypothalamic-pituitary axis. In animal models, ethanol was reported to block the secretion of GnRH in the hypothalamus through reduction of the level of small GTP-binding proteins of the Rab family, which is the key regulator of the membrane and protein trafficking.[70] Increased oxidative stress at the pituitary level was also suggested.[70] The effect of alcohol on T level appears to be controversial, while the low T level was recorded in two previously addressed reports,[63,64] the high level was reported by Jensen et al.[65] The reason for this controversy seems to be due to the difference in the studied population, particularly for the variation in sample size, race, and the possible effect of confounding factors on semen parameters or hormonal level.

It could be concluded that alcoholism has, in general, an adverse effect on male fertility according to the results of those recruited articles. Alcohol addiction produces poor semen quality in terms of sperm concentration, sperm motility, and sperm normal forms. It also causes reduced FSH and LH, but its effect on T level is controversial.

4.6 | 3-Cocaine

Cocaine, a coca extract, is an illicit drug that is widely consumed by addicts worldwide. The addictive criteria of cocaine are related to its effect on dopamine transporters, where it acts as a dopamine reuptake inhibitor.[71] More a more recent report suggests also an affinity to CBR1 and CBR2 in animal models.[72]

A little is known about the impact of cocaine use and male fertility, but in the early report by Bracken et al.(1990),[73] cocaine use among a cohort of 1309 American subjects seeking fertility was associated with an increased risk of low sperm concentration (OR 2.1). These authors reported also that the more the duration of use is associated with decreased sperm concentration, sperm motility, and sperm normal forms (OR 2.0). The same authors also reported that men with sperm counts < 20 million/ml were two times more likely to have used cocaine within the past 2 years than men who had not used cocaine. Also, men with a 5-year or greater history of cocaine use were two times more likely to have low sperm motility. This study was the first to identify the link between cocaine use and sperm parameters. (Level of evidence: 2b).

More than two decades later, Samplaski et al.[74] reported that cocaine users (38 cases, 0.9%) among a large cohort of Canadian men seeking fertility (4400 cases) had little impact on male fertility. However, these results should be taken with caution as other concurrent risk factor and drug abuse was higher in cocaine users versus the whole group of participants. (Level of evidence: 2b).

In an animal model, the mechanism of cocaine-induced infertility was studied by George et al.[75] Cocaine exposure was reported to significantly reduce seminiferous tubules diameters, germ epithelium thickness, increase degenerated cells, and reduced spermatid count in exposed versus non-exposed groups. Since that time, no other studies tried to explore the mechanism by which cocaine abuse affects male fertility until González et al.[76] highlighted a key role for dopamine receptor D1 in mediating cocaine-triggered epigenetic modifications related to the silencing of gene transcription and the histone-to-protamine replacement that controls the chromatin architecture of maturing sperm cells.

Therefore, whether cocaine abuse affects male fertility or not still an open question and further work is still needed.

4.7 | Androgenic anabolic steroid

For several decades, testosterone and its synthetic derivatives have been used for its anabolic and androgenic properties. These substances were first restricted to professional top-level competitive weightlifters, bodybuilders, and track athletes, but become more and more popular among recreational athletes.[77] However, AAS are widely used, not only by athletes in minor-league sports but also by non-athletes as well.[78]

The effect of AAS on male fertility has attracted reasonable attention as many studies tried to address this point many decades before. Overall, 15 articles were recruited that had reported impaired semen parameters &/or hormonal changes in response to AAS.[79–93] This is presented in Table 1.

In general, AAS seems to negatively affect male fertility at the pituitary level, due to its structural similarity to serum T, where it negatively suppresses the FSH and LH secretions.[94] Such changes may be persistent many years after cessation of AAS administration under the effect of reduced INSL3 that may cause persistent Leydig cell dysfunction.[93] It is worth-mentioning here that caution should be taken while addressing relevant studies, because of the generally low level of evidence and the considerable inconsistency in methodology, particularly in terms of the multiple forms of AAS, variations in doses and duration of exposure to AAS investigated. All these factors may alter the results and hence; solid conclusions could be difficult to obtain.

4.8 | Tobacco smoking

Tobacco smoking is probably the most prevalent habit worldwide, and according to the WHO, one-third of adult men in the world are cigarette smokers (http://www.who.int/topics/tobacco/en/). More than 4700 different chemicals have been identified in tobacco smoke,[95] ranging from heavy metals to polycyclic aromatic hydrocarbons and mutagenic chemicals. The addictive nature of tobacco is related to nicotine, and the majority of men who failed to quit smoking are considered as suffering from nicotine dependence.[96–99]

The mechanism by which tobacco affects male fertility had received considerable attention. Earlier, Pacifici et al.[100] pointed out that nicotine, cotinine, and hydroxycotinine levels in the seminal plasma had comparable levels to that of serum in smokers. A significant negative association between these substances and sperm motility was

reported by the authors. Additionally, a significant association between seminal plasma lead levels and lifetime smoking estimate has been reported.[101] Likewise, smoking is considered the most common source of lead and cadmium exposure. Some metal micronutrients involved in the pathogenesis of oxidative stress and male infertility, including arsenic and the aforementioned cadmium and lead, are routinely inhaled during the combustion of tobacco or cigarette paper.[102] Smoking tobacco was also reported to decrease seminal plasma Zn level and Ca^{+2} ATPase that can reduce sperm motility.[103] Moreover, tobacco smoking was reported to increase sperm morphologic damage induced by varicocele.[104]

Besides, animal studies showed that the number of germ cells, Leydig cell, and Sertoli cell was reduced in rat models in this condition.[105] Inline, several ultra-structural defects of testis occur in response to smoking; the basal lamina of the seminiferous tubule is reported to be irregular and thickened in rat testis after daily tobacco smoke exposure.[106] Chronic cigarette smoke was also found to induce apoptosis in mouse testis.[107]

On the molecular level, Xu et al.[108] investigated 31 differentially expressed proteins extracted from the testes of mice exposed daily to cigarette smoke using matrix-assisted laser desorption/ionization-time of flight mass spectrometric analysis. Proteins studied were categorized into five functional clustering groups: metabolic process, cell growth and/or maintenance, RNA and protein processing, stress response, and spermatogenesis. These researchers suggested that phosphatidyl ethanolamine binding protein 1Pebp1 inactivation may affect activation of cell signaling pathway protein extracellular signal-regulated inase could be responsible for the impaired spermatogenesis of mice exposed to cigarette smoking.

Over the past two decades, it seems that there is a global rising of e-cigarette smoking, hoping that smokers were be less harmed by this relatively new method of acquiring nicotine they want with a relative higher safety profile. Actually, this heat not burn (HNB) mood of cigarette smoking actually potentially could affect human fertility as many toxic products present in traditional cigarettes are also present in e-cigarettes but with less concentrations including ROS and lead.[109] Despites that, only one article addressed the impact of e-cigarette on fertility on pregnant mice with reported mild insignificant effect on male offspring.[110]

To address the effect of tobacco addiction on human male fertility, 10 studies of direct relevance to seminal parameters or hormonal changes were recruited.[111–120] This is shown in Table 1.

Considerable variations were observed in recruited articles in terms of the effect of tobacco on both semen parameters and hormonal profile. Despite that the details of these articles—that are shown in provided table- revealed remarkable variations in methodology and findings, it appears that the most consistent effect of tobacco is that its impact on sperm count and morphology. This observation is supported by similar finding of a recent meta-analysis of 16 articles, including 10,823 infertile subjects including (5257 smokers and 5566 non-smokers) by Bundhun et al.[121] The authors reported that oligozoospermia was significantly higher in smokers versus non-smokers. The morphological defect of sperms was also significantly higher in smokers. However, smoking did not affect the pH and sperms motility. Additionally, tobacco smoking did not cause any disturbance in the reproductive hormones. These authors concluded that tobacco smoking was associated with a lower sperm count and an increased number of morphological defects of sperms. However, the pH and the sperm motility, as well as the reproduction hormones, were not affected in this population of infertile men.

In conclusion, despite the plenty of studies that addressed the effect of tobacco addiction on male fertility, accumulated evidence from the results of recruited articles points to the finding that the most consistent effect of tobacco is the sperm count and morphological damage, while its effect on other semen parameters and hormonal changes showed considerable contradictory results.

4.9 | Caffeine addiction

Caffeine (1,3,7-trimethylxanthine) is found in coffee, tea, soft drinks (particularly cola-containing beverages and energy drinks), and chocolate. It easily crosses biological membranes, is rapidly distributed throughout the body, and has been found in saliva, breast milk, the embryo, and the neonate.[122] The caffeine molecule is easily absorbed by humans, having approximately 100% of bioavailability when taken by oral route and reaching a peak in the blood within 15–45 min after its consumption.[123] Caffeine consumption (in coffee, tea, cola, and chocolate) is a daily habit by an uncountable number of men in the world although no adequate estimation of the prevalence of such habit and its impact on male fertility. Sperm DNA damage was claimed as a cause of impaired fertility in response to caffeine intake.[124]

In this review, 13 articles that addressed the impact of caffeine on male fertility were recruited and analyzed and considerable contradictory results were obtained.[66,125–136] Summary of these recruited articles is presented in table 1.

The mechanism by which caffeine produces alteration in semen parameters or hormonal changes is not that clear. Usually, single lifestyle parameters had minor effects on sperm parameter, but the combination of age, BMI, coffee intake, ejaculatory frequency, and duration of sexual abstinence were identified as factors having a negative effect on sperm motility. The negative impact of age, BMI, and coffee intake on sperm quality could be compensated if patients had a high ejaculation frequency and shorter periods of sexual abstinence. It was concluded that the combinations of adverse lifestyle factors could have a detrimental impact on sperm, not only in terms of motility and sperm count but also in terms of sperm head vacuolization. This negative impact was shown to be compensated by higher ejaculation frequency and a shorter period of sexual abstinence. The compensation is most likely due to a shorter storage time in the male gonads, thus reducing the duration of sperms' exposure to ROS.[133]

Marshburn et al.,[125] reported a significantly higher proportion of sperm abnormal forms in men drinking $\geq$ 4 cups of coffee/day (31% vs. 28%). These researchers suggested that caffeine appears to alter sperm motility primarily by inhibition of cyclic adenosine 3′:5′ monophosphate (cAMP)-dependent phosphodiesterase, thus

increasing intracellular cAMP concentration that in turn promotes sperm metabolism.

Radwan et al.[136] failed to find evidence of a relation between DNA fragmentation evaluated by sperm chromatin structure assay and coffee drinking, in 286 healthy men. Coffee drinking was not related to any of the examined parameters of sperm DNA damage and DNA stainability, including the percentages of DNA fragmentation index (DFI), the medium DNA fragmentation index, the high DNA fragmentation index, and the high DNA stainability index.

Therefore, a shortage of adequate information about the exact effect of caffeine on male fertility is still present, regardless of the relative good number of relevant studies and the wide consumption of caffeine by millions of young men.

5 | DISCUSSION

In the current review, the importance of different addictive substances, in terms of their effect on male fertility, was variable from one country to another as it is the complex sum of many social, cultural, legal, and even spiritual considerations. This explains the focusing of scholars in particular areas of the world on studying certain substance use disorders and their impact on male fertility, despite its variable relative importance that could be less- or more- significant in another area.

The most relevant substances that attracted attention were tobacco, opioids and cannabinoids, caffeine, alcohol, and AAS. On the other hand, tramadol and cocaine received a lower level of attention from scholars, despite their detrimental effects on the men's health and quality of life.

Most of the reviewed articles succeeded to demonstrate the deleterious effect of substance use disorders on male fertilizing capability, at various levels of evidence. In this context, ethical considerations could explain the scarcity of recruited randomized controlled trials that have a higher level of evidence, compared to either case controlled or cross-sectional studies, that could be conducted to address the effect of a substance with well-known addictive properties on humans. It is unethical to give such substance deliberately to human subjects and expose them to the hazards of addiction. Alternatively, cohort studies-midway in its level between randomized controlled trial and case-controlled or cross-sectional studies—could be a logic solution. In cohort studies, the addicts, already taking the drug in question, could be recruited from the cohort and investigated for the impact of such substance on their health, including its specific effect on their fertility.

A particular highlight should be also focused on the complex nature of male fertility. It is worth-mentioning here the possible interaction between confound factors affecting male fertility that may form a sort of synergism in terms of its hazardous effect on human fertility. Usually, an infertile male, even presenting with major cause of infertility like varicocele, could also has other risk factors such as smoking, alcoholism, etc., that could aggravate the condition. This may represent a further challenge during conducting studies that address the relation between male fertility and a specific risk factor like addiction. A proper methodological standardization is thus needed. In the current review, as an example, the effect of these confound factors that can affect fertility was not ruled out in almost half of recruited articles. Moreover, confound variables effect were adjusted statistically by logistic regression analysis in only six of the reviewed articles.[73,92,118,127,130,134] This may lead to a sort of bias in the obtained results in remaining studies that did not take these points into consideration.

Overall, most of recruited articles demonstrated the negative effect of many addictive substances on male fertility. From the practical point of view, two targets should be warned here. First, the clinicians, who should be aware of such effects and exerts more effort during their clinical approach for diagnosis and treatment of male infertility. The second target here should be the consumers of these products that should be properly approached and then warned against the possible negative effects of such substances through suitable channels of communications, including social media. We suggest here for our colleagues who are interested in this field to provide laymen abstracts of their work and try to publish them in the widely seen social media that could be very helpful for such purpose.

6 | CONCLUSIONS

Addiction has a variable, but generally negative, impact on male fertile capabilities. Most of the addressed studies demonstrated such negative relations at different levels of evidence. More future studies are needed after a proper methodological and statistical approach, including logistic regression analysis, to predict the effect of a specific substance use disorders on male fertility. More attention should be made to this rapidly growing disorders in terms of their impact on men's health, including fertility, and increasing both clinicians and public awareness could be very helpful to combat this pattern of behavior.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHORS' CONTRIBUTION

Both authors (Alghobary M and Mostafa T) contributed equally in all steps of this manuscript including; study design, data acquisition and interpretation, making the draft and final revision.

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How to cite this article: Alghobary M, Mostafa T. Addiction and human male fertility: A systematic review and a critical appraisal. *Andrology*. 2022;1–23.
https://doi.org/10.1111/andr.13196