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# Drug abuse and reproduction

Sandro GIARDINA and Bruno BECCA

*Divisione di Ostetricia e Ginecologia, Unità di Fisiopatologia della Riproduzione, Ospedale Civile di Ravenna, Italy*

**Summary.** - The spreading of drugs in the western world has increased dramatically, especially among young people. Over 10% of the population of the USA in reproductive age uses cannabinoids, cocaine, heroin or other drugs. Data related to Italy indicates a progressive increase in cocaine abuse, that adds up to the already dramatic rise in heroin and alcohol abuse. Although the research work on the reproductive effects of drugs has started recently and is still limited, the damages that they can cause to endocrine system, pregnancy and conceptus are clear.

*Key words:* drug abuse, reproduction, pregnancy.

**Riassunto** *(Abuso di droga e riproduzione).* - La diffusione delle droghe d'abuso nel mondo occidentale ha assunto dimensioni drammatiche, soprattutto nella popolazione giovanile. Negli USA ormai oltre il 10% della popolazione in età riproduttiva assume cannabinoidi, cocaina, eroina o altre droghe. I dati relativi all'Italia indicano un progressivo aumento dell'abuso di cocaina, che si aggiunge a quello già drammatico di eroina e di alcool. Sebbene la ricerca sugli effetti riproduttivi delle droghe sia recente, e ancora limitata, sono ormai evidenti i danni che esse possono provocare nel sistema endocrino, nella gravidanza e nel prodotto di concepimento.

*Parole chiave:* abuso di droga, riproduzione, gravidanza.

The term "drug" includes substances that differ a lot one from the other based on their chemical nature, pharmacological action, toxicity and clinical significance.

According to a syntomatological criterion, drugs can be divided into 3 subgroups based on their impact on the central nervous system (CNS):

1) depressing CNS's activity;
2) stimulating CNS's activity;
3) psychedelic [1] (Table1).

Besides the so-called "illegal" drugs, this classification also includes the "legal" drugs such as alcohol that, though entailing high reproductive risks, do not receive sufficient attention by the public opinion. Notwithstanding its recognized teratogenic effects, in the western world alcohol can even be defined as an environmental element, "an ecological factor", such as coca in Perù and cannabis in India [2].

The World Health Organization (WHO) defined drug addiction as follows: "State of periodical or chronic intoxication that is noxious to man and society, caused by the repeated consumption of (natural or synthetic) drugs, having the following features:

1) an invincible desire or need to use the substance and procure it by any means;

2) tendency to increase dosage (tolerance);

3) psychical, and/or physical dependency on the effects of the substance, with onset of withdrawal syndromes when it is no longer used".

It is to be precised that one of the references used recently to define the danger of an excessive use, namely physical dependency, did not prove to be sufficient to define the addictive character of drugs. Actually psycological dependency - that is difficult to be diagnosed and quantified in man - often played a decisive role in the framework of the overall behaviour of an individual. Consequently it is now preferable to refer to "dependency" without any adjective (Table 2) [1].

The ability of these substances to cause psychical and physical dependency phenomena takes on an important clinical significance in reproductive physiopathology. This is due to the fact that even factors entailing high responsibilities - such as reproduction and pregnancy - can have no effect of inhibiting their use [2].

From the epidemiological point of view there was a sharp increase in the spreading of drugs over the last few years.

At least 30% of the American population over 12 years of age reports using cannabinoids, cocaine, heroin or psycotropic drugs. The National Institute on Drug Abuse (NIDA) estimates that 56 million American women between 15 and 44 years of age have used drugs. Cocaine in particular had a dramatic diffusion recently. NIDA estimates that at least 10% of the American population in reproductive age has used them [3]. The phenomenon of "narcotics" has nevertheless spread world-wide. Prof. V. Prokorvsky, President of the Academy of Medical Sciences of ex-URSS, presented impressive data to the

**Table 1.** - Pharmacological classification of the major psycoactive drugs

| Substances depressing the CNS | Substances stimulating the CNS | Psycodysleptics or hallucinogens |
|---|---|---|
| Ethyl alcohol | Cocaine | Cannabis *(*)* (hashish, marijuana) |
| Inhalants, organic solvents | Amphetamines caffeine | Hallucinogens (LSD, mescaline, psilocybin, scopolamine) |
| Narcotics, (opiate morphine, heroine) | Anti-depressants | |
| Barbiturics | | |

*(*)* Cannabis causes typical effects that are partly comparable with those of the psycodysleptic drugs.
(CNS= Central Nervous System).

**Table 2.** - Drugs generally used which causes physical and psycological dependency as well as tolerance

| Drugs | Physical dependency | Psycological dependency | Tolerance |
|---|---|---|---|
| **Substances depressing the CNS** | | | |
| Opioids (morphine, heroin, etc.) | ++++ | ++++ | ++++ |
| Barbiturics | +++ | +++ | ++ |
| Other hypnotic sedatives | +++ | +++ | ++ |
| Ethyl alcohol | +++ | +++ | + |
| Meprobamate | +++ | +++ | + |
| Benzodiazepines | + | +++ | + |
| **Substances stimulating the CNS** | | | |
| Amphetamine, methamphetamine, similar drugs | + | +++ | ++++ |
| Cocaine | -/+ *(a)* | +++ | + *(a)* |
| Tobacco (nicotine) | -/+ | +++ | + |
| **Hallucinogens** | | | |
| LSD *(b)* | - | ++ | ++ |
| Mescaline | - | ++ | + |
| Cannabinoids (low THC dose) *(c)* | - | ++ | + |
| Cannabinoids (high THC dose) *(c)* | - | ++ | ? |

*(a)* Dose depending, at high doses; *(b)* LSD: dietylamide of lysergic acid; *(c)* THC: tetrahydrocannabinols; (-) no effects; (+) slight effects; (++++) marked effects.

Vatican Conference that took place in Rome from November 21 to 23, 1991: 15-20% of Soviet students make use of narcotics. In Italy there are approximately 60,000 individuals being treated in Public Services for Drug Addicts. Reliable sources estimate, however, that there are at least 400,000 drug addicts in our country [1]. The spreading of drugs in Italy seems to be progressively on the increase with some peculiarities. Data related to drug seizures (heroin and cocaine) in Italy from 1980 to 1990 show that the illegal market of drugs is characterized by an ever increasing demand for cocaine, that did not replace the traditional one for heroin, but was rather superimposed and added to it (Fig. 1). Moreover there seems to be an increase in the consumption of cannabinoids (Fig. 2).

Another peculiar feature of the Italian situation is the diffusion of AIDS among drug addicts. In the USA and Northern Europe the absolute majority of AIDS cases is observed in the risk group of homosexuals/bisexuals (73.4%), while those taking drugs i.v. account only for 17%. In Italy, on the contrary, the major risk group is that of drug addicts, representing 60-70% of all cases.

In addition, 55.5% of AIDS pediatric cases concern the children of drug-addicted mothers [4] (Table 3).

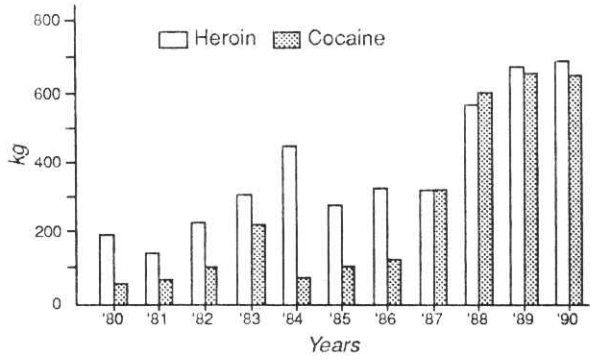


**Fig. 1.** - Seized drugs, kg (heroin-cocaine) in Italy 1980-1990 (31 October).
Source: Drug enforcement service, Ministry of the Interior. Data processed by: Drug abuse section, Istituto Superiore di Sanità.

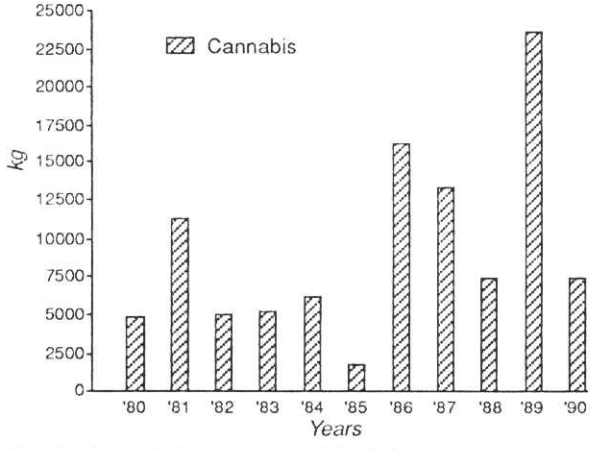


**Fig. 2.** - Seized drug, kg (cannabis) in Italy 1980-1990 (31 October).
Source: Drug enforcement service, Ministry of the Interior. Data processed by: Drug abuse section, Istituto Superiore di Sanità.

## Limits of research work

The study of the relationship between reproductive pathology and drugs is very difficult and complex; there are several factors contributing to this, such as:

a) the presence of a rarely homogeneous population (e.g. according to age and period of use);

b) the frequent multiple drug addiction;

c) concomitant hyponutrition, vitamin deficiencies and metabolic changes due to liver and tissue lesions that are often present in drug addicts;

d) physical state of the drug abused, methods of use, dosage, how it is introduced into the body (orally, i.v., subcutaneously, sublingually, smoking, "sniffing", etc.);

e) the presence in the "street drugs" of several "substances to be mixed", that are often more harmful to health than "pure" substances (Table 4) [1, 5].

In a study performed in Ravenna in 1988, the content of heroin in street bags ranged only from 0% to 20% of the total content [1, 2]. Lastly, a reproductive anomaly can be investigated only when fertility is desired. For these reasons it is difficult to explore the negative effects of drugs on reproduction and they might not be identified for several years [5].

## Opiates

Opium is made up of the exudate (lattix) derived from the immature seminal capsules of "Papaver somniferum", a local plant of Asia Minor, that is now "grown" - either legally or illegally - also in several other nations, namely: India, China, Turkey, URSS, Hungary, Iran, Balkan States and some African nations.

Opium ("poppy juice") has been known since ancient times due to its powerful anti-diarrhoeal activity; its analgesic activity was well coded starting from the XVIIth century.

Opiates are substances of natural (extracted from vegetables) or synthetic origin having an analgesic-narcotic action, that has an impact on morphine receptor and is capable of relieving or abolishing painful feelings with a central mechanism. Said substances are called opiates (opioids) because they have - partly or wholly - the properties of opium.

The abuse of opium, either taken orally or smoked, had a huge diffusion in the last century, both in the East and some western countries, both for voluptuary and medical use.

Following the identification of its most active principle, morphine (in 1803), as well as the introduction of the hypodermic needle (in 1857), and the international legislative restrictions, its diffusion decreased steadily until it almost disappeared. It was replaced by extractive opium-narcotic substances of total chemical synthesis [1, 6].

Over the last decades, heroin had a dramatic diffusion in the world. It is obtained by double acetylization of two morphine hydroxylic groups. Heroin's effect is felt more rapidly than other opiates. Although its action lasts less than that of morphine, it keeps all its effects unchanged and creates a more intense euphoria (the so-called "flash"), that is the effect particularly appreciated by heroin drug addicts. Heroin's half-life in the body is 1-1.5 hours, while that of morphine is 2.5-3 hours.

Heroin can be ingested, smoked, "sniffed", taken on parenterally (i.v. or subcutaneously) or inhaled through the fumes released by an overheated metal plate where heroin is mixed up with caffein according to a Chinese method named "chasing the dragon".

Among all parenteral self-administration methods, the most widespread is notoriously i.v. With regard to dose preparation methods, it must be pointed out that heroin, purchased in powder, is dissolved in water, often without any hygienical precaution [1, 6, 7].

**Table 3.** - Distribution of AIDS cases according to type of transmission and sex notified in Italy at 30 September 1991

| Transmission | Male | Female | Total | (%) |
|---|---|---|---|---|
| Homosexuals | 1090 | 0 | 1090 | 10.5 |
| Bisexuals | 498 | 0 | 498 | 4.8 |
| Drug addicts | 5592 | 1370 | 6962 | 67.2 |
| Drug addicts and homosexuals | 136 | 0 | 136 | 1.3 |
| Drug addicts and bisexuals | 144 | 0 | 144 | 1.4 |
| Haemophiliacs | 123 | 1 | 124 | 1.2 |
| Transfusions | 92 | 62 | 154 | 1.5 |
| Heterosexuals | 328 | 367 | 695 | 6.7 |
| **Total adults** | 8452 | 1894 | 10346 | |
| Sons of mother | | | | |
| - TD | 62 | 70 | 132 | 55.5 |
| - heterosexual contact | 35 | 35 | 70 | 29.5 |
| - transfused | 2 | 1 | 3 | 1.3 |
| - not defined | 3 | 8 | 11 | 4.6 |
| Haemophiliacs | 13 | 0 | 13 | 5.5 |
| Transfusions | 2 | 5 | 7 | 2.9 |
| Not defined | 1 | 1 | 2 | 0.8 |
| **Total pediatric cases** | 118 | 120 | 238 | |
| **Total** | 8570 | 2014 | 10584 | |

*Heroin and endocrine-reproductive system*

After crossing the haematoencephalic barrier, heroin has a toxic action on the hypothalamus and alters the neuroreceptors of the dopaminergenic and adrenergic systems. Consequently, there is a decrease in basal levels and the pulsatility of hypophyseal gonadotropic hormons LH and FHS, and an increase in LTH or prolactin [5]. LH and FSH act on the testis in men and on the ovary in women. Hence, their decrease inevitably entails an alteration of reproductive functionality, with negative consequences on the production of testosterone and maybe on spermatogenesis in men, with irregularities of the menstrual cycle and frequent anovulation in women.

Prolactin increase causes impotence in men, menstrual cycle alterations with possible galactorrhea in women.

It is interesting to note that said actions are directly correlated to the quantity of drug used [2, 5, 8].

A decrease in total testosterone levels and in particular its free quota - that is considered as the part having a metabolic action - is frequently observed. The administration of naloxone, a receptor antagonist of opiates, causes a rise in LH plasma levels [2, 5, 8].

In female drug addicts there is a sharp reduction in fertility. This is attributable to: 1) menstrual cycle irregularities (oligoamenorrhea, polymenorrhea and hypermenorrhea) with anovularity and alterations of the luteal phase of the menstrual cycle; 2) pelvic flogoses, due to non-compliance with hygienic norms, frequent prostitution and decrease in endogenous defence mechanisms [2, 7].

Female drug addicts are however less prepared to use contraceptive techniques because they are used to frequent amenorrheas as well as concomitant pathologies (flebitis, hepatitis, pelvic phlogosis), that are often contra-indications to the safest contraceptive methods (pill, IUD) [2].

*Heroin and pregnancy*

Heroin abuse during pregnancy may be responsible for several medical complications both in the mother and the fetus [7, 9].

Maternal complications derive mostly from life-style, administration method, drug used and substances to be mixed included in it. Frequent complications are the following:

1) infectious diseases (pneumonia, endocarditis, hepatitis, pyelonephritis) due to the use of contaminated solvents and syringes, allowing for the penetration of micro-organisms into maternal circulation (staphylococci, streptococci, clostridia, mycosis, viruses, etc.);

2) sexually-transmitted diseases (vaginitis, gonorrhea, syphilis, HSV, chlamydia HIV, condyloma);

3) anemia, probably due to nutritional deficiencies;

4) gestosis.

Frequent embryo-fetal complications are:

1) abortion;

2) prematurity;

3) growth defects;

4) perinatal mortality [2, 7, 9].

**Table 4.** - Substances to be blended to prepare "street drugs"

| | |
|---|---|
| amphetamine | parathion |
| arsenic | phencyclidine |
| barbiturics | procaine |
| butacaine | quininerubber |
| caffeine | starch |
| cotton | sulphuric acid |
| cyanides | strychnine |
| fibres | talc |
| maltose | wall powder |
| nicotine | |

There seems to be no association between prenatal exposure to heroin and the onset of congenital malformations [8]. Pulmonary maturation of the fetus is usually anticipated [7].

50-70% of infants have a withdrawal syndrome including: generalized hyperactivity, course tremors, irritability, respiratory disorders, fever, nasal congestion, vomit, diarrhea, hyperfagia and rarely convulsions [9, 10].

A few studies are available on the long-term postnatal effects in infants with heroin-addicted mothers on their intellectual and learning capacities as well as their neuro-behavioural development, including disposition to drug-addiction when young or adults [9].

It is in fact difficult to assess precisely the interferences due to the co-factors of the often degraded environment experienced by said children during their childhood.

The drug addicts that inject drugs i.v. are the major AIDS risk group in Italy, accounting for 60-70% of all cases [11].

The prevalence rate of anti-HIV antibodies in drug addicts of the main Italian cities is 30-40%. Hence, in Italy pregnancy among heroin addicts is dramatically associated with HIV infection [11]. The frequency of perinatal transmission of infection ranges from 14% to 35% according to the epidemiological situation of the populations studied. Another 25% approximately of infants is positive to HIV test, due to the presence of a passive immunity of maternal origin [4, 12]. This "false positiveness" usually disappears within 15 months from birth. The presence of antigen P24 is a sign of active infection, while its absence is not a sign of a state of negativeness [11, 12]. Virus transmission seems to occur more frequently close to delivery, but other periods - such as the postnatal period through breast-feeding - are not excluded. The clinical stage of pregnant women seems to affect the possibility of transmission. In particular, women with absolute values of lymphocytes $CD4^+$ lower than $400/mm^3$ appear to have a higher risk of transmission [4, 11-13].

Though the suspension of the use of heroin does not entail any particular problem in women who have not yet developed physical dependency, the sudden interruption of drug uptake in female drug addicts, with the consequent withdrawal syndrome, can entail fetal suffering or even death. For the same reasons the use of opiate antagonists (e.g. naloxone) is contraindicated in pregnancy, if not to save mothers' lives [2]. At present the treatment of heroin-addicted pregnant women is based on the use of methadone, a long-action synthetic opioid that can be administered orally. Methadone, having morphine-like psycotropic effects and blocking need, can reduce the risks related to i.v. intake of "street drugs" and allow health care structures to better control pregnant women [9]. Various treatment schemes have been proposed, envisaging a gradual detoxification or continuing to take the drug at low dosages, after identifying posology based on the daily quantity of drug taken and the onset of withdrawal symptomatology [9, 10].

Methadone does not seem to have teratogenic effects, while it was associated with a greater frequency of hyperbilirubinaemia, respiratory depression and withdrawal syndrome in infants [10].

## Ethyl alcohol (or ethanol)

Alcohol abuse is one of the plagues of modern society. Even though the related medical and psyco-social problems have become reasons for concern of political and health care institutions of several countries in the world, there are many hindrances to the evaluation of the size of the phenomenon and the implementation of efficient preventive and therapeutical measures.

It is difficult to calculate the incidence of alcohol abuse and dependency in Italy, that is one of the major wine-producing countries in the world. At present Italy ranks first in Europe for average per-capita consumption of wine and spirits with 120 liters/year. Reliable sources based on trade consumption data estimate that there is about one million alcohol addicts in Italy [1].

Unfortunately the mass media (television, newspapers, etc.) are full of winning messages launched by manufacturers advertising wines and especially spirits "to be drunk anywhere in bars, at home, alone or with friends", considered as status symbols, and shown along with images of fast cars, beautiful women and smart young men.

It would be advisable to have regulations on advertising messages, at least to reduce their danger, if only by adding recommendations on "maximum doses per day", or "contra-indications". There is in fact also the dramatic reality of "saturdays' evening massacres", cyrrhosis, pancreatitis and many other alcohol-related pathologies, including reproductive diseases, that should neither be ignored or underestimated.

### *Ethyl alcohol and endocrine-reproductive system*

Acute or chronic abuse, both in men and animals, causes a decrease in plasma testosterone levels with mechanisms at hypothalamic, hypophyseal and gonadic, as well as hepatic levels.

This hormone is particularly important in man because, besides promoting the differentiation of male genitalia in intrauterine life and their development in the puberal age, it has a general anabolic action with the development of muscular masses and skeletal segments. Moreover, it affects sexual attitudes of individuals of both sexes [2, 5].

A testicular hypotrophy was observed in chronic alcohol addicts, with an increase in plasma estrogen and prolactin concentrations, associated with gynecomastia, decrease in libido and impotence [5].

The decrease in sexual vigour is often accompanied by projections of one's own insufficiency onto the partner (jealousy delirium).

Besides, oligospermia and morphological alterations of spermatozoa were observed.

The chronic abuse of alcohol in women causes oligomenorrhea and anovularity, with subsequent fertility reduction [2, 5].

*Ethyl alcohol and pregnancy*

A teratogenic action of alcohol was assumed since ancient times. It is known that among the inhabitants of Carthagen the bride and the groom were not allowed to make use of spirits during the wedding-night to avoid any malformation in the possible conceptus. The correlation between incidence of congenital malformations and the so-called "gin epidemic" is also known; it occurred in England between 1720 and 1750 with the liberalization of liquor. However it was only Lemoine in 1968 and Jones *et al.* in 1973, who drew the attention of the international scientific literature to a fetal clinical pattern that could be correlated to the abuse of spirits in pregnancy, defined as "Fetal Alcohol Syndrome", characterized by:

1) pre and postnatal growth retardation;

2) dysfunctions of the central nervous system, such as microcephaly with mental retardation, poor coordination, hypotonia, deambulation and language retardation, behavioural modifications;

3) typical cranio-facial alterations, such as short palpebral fissure, microphtalmia, hypoplasic filter, turned-up nose, thin upper lip, micrognathia, upper maxillary hypoplasia, ptosis and strabismus, incomplete development of the upper helix of the ear;

4) heart abnormalities, such as anomalies of the great vessels, interatrial and interventricular communications;

5) minor associated clinical characteristics, such as renal anomalies, genital anomalies (hypoplasia of labia majora, cryptorchidism, hypospadias) skeletal (radio-ulnar synostosis, clinodactylia) and muscular anomalies (hernias) and others [14-16].

There are no epidemiological data on the incidence of Fetal Alcohol Syndrome in Italy. In western countries its incidence is calculated at 1-2 cases per 1000 infants [1, 17].

WHO's experts also point out a growing consumption of spirits in young people and women in the western world.

The literature available at the moment does not allow us to precisely define either the quantity of alcohol to be considered as excessive or the one which is harmless during pregnancy [16-20].

In a study on 9,000 pregnant women Kaminsky *et al.* demonstrated that the consumption of 450 ml of wine per day entails a high risk in pregnancy, with increasing abortion and stillborn rates [15].

At present there is the tendency to attribute teratogenic effects to a direct toxicity of ethanol and its metabolites. Acetaldehyde - that the fetus cannot metabolyze because it is deprived of the specific dehydrogenase - seems to be more toxic than ethanol itself [2, 20].

Its action would consist in inhibiting the replication of RNA and cytoplasmatic transcription systems, with a decrease in proteic synthesis [2, 16, 20].

Other elements may contribute besides direct toxicity, namely:

a) maternal malnutrition due to chronic alcoholism; b) other associated toxic factors, such as tabagism or the use of tranquilizers or opiates; c) serum zinc deficiency [2].

**Cannabinoids**

The major psycoactive cannabinoid is delta-9-tetrahydrocannabinol, generally abbreviated as "THC", that is contained in cannabis leaves and inflorescences. THC is highly lipophilic and easily accumulates in body fats where - following relevant or extended intakes - it can reach saturation levels. This feature explains why very long urinary elimination times are observed for those substances [1].

Several cannabis-based preparations are available on the market. Hashish and marijuana, as well as hashish oil, are generally taken by smoking, after being mixed up with tobacco, in cigarettes prepared by consumers by hand or, less frequently, ingested in the form of cakes or infusions [1].

Consumers' subjective symptoms are: euphoric state (associated with gaiety, talkativeness, merriment, pleasant hallucinations), feeling of psyco-physical well-being, increased appetite, distorted time and space perceptions. Besides the effects on the CNS, the major and more easily measurable physiological effect in man is an increased heart rate [1].

*Cannabinoids and endocrine-reproductive system*

Experiments on laboratory animals showed that delta-9-tetrahydrocannabinol, the main psyco-active component of cannabinoids, inhibits the secretion both of hypophyseal gonadotropines LH and FSH and

prolactin, with a consequent alterated production of sexual steroid hormons. The inhibitory effect seems to occur at hypothalamic level [5].

In Rhesus monkeys the acute administration of tetrahydocannabinol in the follicular phase of the menstrual cycle inhibits ovulation. An acute administration in the post-ovulation phase may shorten luteal phase duration. Menstrual cycle irregularities ensue (amenorrhea, polyamenorrhea); they often last several months, even after discontinuing treatment. In case of chronic administration, owing to the onset of the "tolerance" phenomenon, the menstrual cycle tends to return to normal [5].

In male laboratory animals both acute and chronic administrations of cannabinoids lowers testosterone serum concentrations.

Some studies performed in man showed a decrease in serumal testosterone levels [5]. Studies carried out on men and animals however found an association between the chronic abuse of cannabinoids and a reduction in spermatozoa number and motility [5, 10].

An increase in the number of morphologically-altered spermatozoa was also pointed out [10].

*Cannabinoids and pregnancy*

Cannabinoids are the illegal drugs most frequently used by women in reproductive age. Nevertheless, little is known about their effects on pregnancy and the long-term effects of prenatal exposure [3].

In the United Stated 10-16% of women used cannabinoids in the early phases of pregnancy.

Tetrahydrocannabinol crosses the placenta; owing to its slow metabolization, even an occasional use can be accompanied by a long fetal exposure. Several studies showed a greater frequency of prematurity, immaturity, fetal suffering and low birth weight infants with neuro-behavioural disorders among pregnant women using high doses of cannabinoids [3, 5, 21].

Nevertheless, further studies are needed to establish the long-term effects of prenatal exposure to cannabinoids. Research work is in fact largely affected by methodological problems and an inadequate control of co-variants (i.e. poly-drug addiction) [2].

## Cocaine

Cocaine is an alkaloid contained in quantities ranging from 0.4 to 2.5% in "coca" leaves (erythroxylon coca), a plant originating from Latin America (Equador, Perù, Bolivia, Chile).

For several centuries the "Indios" chewed coca leaves to relieve pain due to fatigue and malnutrition. This habit still persists today, but the harvest of huge plantations is almost totally used to produce pure cocaine to be shipped to USA, Europe and Japan.

This drug can be taken either orally or i.v., but the most frequent administration techniques are nasal inhalation of powder ("sniffing") or inhalation of vapor.

I.V. injection allows for the highest use of the drug and its quickest action. This practice is therefore more frequent now than in the past, sometimes associated with heroin ("Speed-ball mixture"). In this case sympathicomimetic effects are noticed starting from very low drug doses, of about 4-10 mg i.v. [1].

Recently "crack" is being used, especially in the USA. It is an unexpensive mixture of cocaine hydrochloride and sodium bicarbonate. When smoked together with tobacco in sigarettes or adequate (water-cooled) pipes it is very effective, because the free cocaine molecule ("free-base") is released during combustion and immediately made bioavailable to brain receptors [22, 23].

Cocaine stimulates the central nervous system, and blocks the presynaptic "reuptake" of nor-epinephrine and dopamine. Consequently, there is an increased concentration of catecholamines in nerve endings causing vasoconstriction, tachycardia, hypotension, hyperthermia.

Cocaine raises the mood and resistence to fatigue, entails an euphoric excitement, decreases the feeling of hunger and especially increases sexual potency and desire [1, 24].

When taken in high doses, the initial excitatory phase is often followed by a depressive phase. The lethal cases of cocaine abuse are due to strong respiratory depression or cardiac arrest.

The main metabolite observed in human urines is benzoil-ecgonine [2, 24].

*Cocaine and endocrine-reproductive system*

Studies performed on ovariectomized female rats showed that cocaine increases LH values when used at low or moderate doses, while at high doses inhibits its release [2, 5, 7]. Cocaine abuse does not seem to affect FSH release, while instead entails a steady fall of PRL levels [7]. On this experimental basis testosterone levels should theoretically be increased after using a medium-low dose, while they should be diminuished after using high quantities. However, there are no studies on cocaine effects on reproductive hormons in humans, also due to evident ethical-deontological implications. Hence, little is known about the possible endocrine-reproductive alterations that this drug might cause both in men and women [2, 5, 7, 24].

*Cocaine and pregnancy*

The dramatic increase in cocaine abuse by the general population of the United States that occurred over the last decade, involved also the population of females in reproductive age.

In that country recent epidemiological surveys performed in several Hospitals indicated a prevalence of cocaine abuse among pregnant women ranging from 8% to 17% [25-27]. In Italy indications of cocaine abuse during pregnancy are still occasional, but expectations are pessimistic, owing to the rapid diffusion of this drug among the general population.

Moreover, pregnant women using drugs tend not to report to their doctors. In a multicentric study carried out in the United States, only one pregnant woman out of four - among those with a positive result at laboratory tests - admitted using drugs [28-31].

Cocaine entails a rapid rise of catecholamines, whose cardiovascular effects can seriously compromise feto-placental unit [32].

The risk increases if the drug is taken i.v. or through "crack" vapours; crack is a cocaine alkaloid that is very much popular thanks to its low cost, as well as its rapid and intense action [23, 33].

Several epidemiological studies established a significant correlation between cocaine abuse during pregnancy - even though occurring only during the first three months - and higher frequency of:

- abortion;
- fetal death;
- placentar abruptio;
- low birth weight;
- acute and chronic fetal distress;
- prematurity;
- congenital malformations (microcephaly, cardiac, genitourinary and gastrointestinal abnormalities) probably due to district vasoconstrictions during intrauterine development [32-39].

Infants often suffer from withdrawal syndrome (tremors, irritability, uncontrollable weeping, muscular rigidity, tachypnea, tachycardia) and can later on suffer from neuro-behavioural disorders.

In particular infants born after prenatal exposure to cocaine seem to have a very high incidence (about 15%) of "Sudden Infant Death Syndrome" (SIDS) [40, 41].

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