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Drug abuse and reproduction

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Drug abuse has so permeated our society that the use of marijuana, alcohol, cocaine, and other mood-altering substances has become commonplace among young adults (Table 1).[1] Today, an estimated 5% to 10% of women of childbearing years (more in some sociodemographic groups) use illicit drugs on a regular basis, and 5% are classified as "heavy" drinkers of alcoholic beverages (two or more drinks per day).[2] Although the research on the reproductive effects of drug abuse is relatively new, it shows potentially serious risks to reproduction and fertility.

REPRODUCTIVE RISKS OF DRUG ABUSE

The degree of reproductive risks from drug abuse depends on many factors. A major factor is extent of drug use, i.e., the amount of a drug that is taken, its frequency of use, and the amount of active ingredients (and contaminants) in the street drugs. A single episode of drug intoxication carries much less risk to reproductive hormones than does daily use. Another factor is the age of the user and the length of time the drug is used. Frequent drug use in adolescence or any drug use during pregnancy is potentially more hazardous. Additionally, individuals with hypogonadal syndromes may be at increased risk to the damaging effects of these drugs.

The reproductive system is unusual among the bodily systems in the complexity of the mechanisms that control it and that must operate in order for it to function. Many classes of drugs can disrupt aspects of these controlling mechanisms and thereby alter reproductive function. Drugs that disrupt nervous system function (either voluntary or autonomic) can inhibit reproduction. The hypothalamic nervous pathways that control the secretion of gonadotropins are inhibited by such central nervous system (CNS) drugs as marijuana, the narcotics, barbiturates, and tranquilizers, making these pathways a major mechanism for the effects of drugs on reproductive hormones. Other classes of drugs include those that inhibit protein or nucleic acid synthesis or cell division; agents that inhibit endocrine or exocrine secretion mechanisms; and agents that alter the biotransformation of hormones by the liver. Few other bodily systems require the intricate interaction of so many components for efficient operation. However, disruption of reproduction is a subtle process that may only be detected when fertility is desired. For this reason, drug effects on reproduction in a population may not be detected for many years.

LIMITATIONS ON REPRODUCTIVE RESEARCH WITH DRUGS OF ABUSE

Almost all drug abuse research has been fraught with contradictions and controversies. Research on the reproductive effects of drugs has had numerous methodologic and interpretive problems, and several important questions remain unanswered. Because ethical considerations prohibit controlled human experiments in this area, clinical research has been limited to epidemiologic and retrospective studies, case reports, and small studies of volunteers. Controlled human studies seldom have been done. Regulations prohibit administration of drugs of abuse to women who might become pregnant or to anyone who has not previously used the drug. The life-styles of regular drug abusers frequently involve conditions that may be hazardous to gen-

Table 1 Current Drug Use by Age Group[a]

Drug	Age group	1979	1982	1985
	yrs	%	%	%
Alcohol	12–17	37.2	26.9	31.5
	18–25	75.9	67.9	71.5
	26+	61.3	56.7	60.7
Marijuana	12–17	16.7	11.5	12.3
	18–25	35.4	27.4	21.9
	26+	6.0	6.5	6.2
Stimulants	12–17	1.2	2.6	1.8
	18–25	3.5	4.7	4.0
	26+	0.5	0.6	0.7
Cocaine	12–17	1.4	1.6	1.8
	18–25	9.3	6.8	7.7
	26+	0.9	1.2	2.1
Hallucinogens	12–17	2.2	1.4	1.1
	18–25	4.4	1.7	1.6
	26+	<0.5	<0.5	<0.5

[a] Percent of the overall household population reporting drug use within the past month at the time of the survey (highlights of the 1985 National Household Survey of Drug Abuse, National Institute on Drug Abuse[1]).

eral health and reproductive health, such as poor nutrition, inadequate medical care, use of contaminated drug paraphernalia, and multiple drug use. These investigations also entail problems of adequacy of the endocrine data collected, validity of self-reports of drug use, and possible bias in participant interviews. Such confounding variables have made it difficult to detect disruptive effects on reproductive function and to document associations with drug abuse practices.

Many of the studies of drug effects on reproduction have been done using laboratory animals. In our opinion, the best animal model for the study of drug abuse effects on reproduction has been the nonhuman primate. Most of the reported drug-effects animal studies have been confirmed by clinical observations, although there have been examples wherein the magnitude of the drug effect has not been that predicted in animal studies. Some of the early studies in laboratory animals used drug dosages far in excess of those used by humans and reported devastating disruption of reproductive function. Recent developments in assay technologies have provided the means to measure blood concentrations of the various drugs, so that the drug dosages used in laboratory studies can actually reflect the usual pattern of drug use by people. Recent advances in our knowledge of hypothalamic-pituitary-gonadal function also have provided important new insights into how the drugs produce their effects. These new developments have resulted in more accurate and reliable data and greater collaboration among laboratory and clinical studies.

NEUROACTIVE DRUGS AND HYPOTHALAMIC-PITUITARY-GONADAL FUNCTION

The evidence now strongly indicates that the major pathways involved in the hypothalamic control of gonadotropins are adrenergic and dopaminergic. A multitude of pharmacologic agents can modify neurotransmitter levels by altering synthesis, release, receptor activation, and reuptake. The best known drugs that produce actions of this type are the neuropharmacologic agents that either inhibit CNS activities—the anesthetics, analgesics, sedatives, and tranquilizers; or stimulate CNS activities—the antidepressants, stimulants, and hallucinogens (Table 2). These drugs can modify the hypothalamic-pituitary control of the gonadotropins and prolactin (PRL) because of their action on CNS pathways. The changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and PRL concentrations can result in adverse side effects on the reproductive system, including

Table 2 Pharmacologic Classes of Drugs of Abuse

- CNS stimulants
  - Amphetamines
  - Caffeine
  - Cocaine
  - Nicotine
  - Phenmetrazine (Preludin[a])
- CNS depressants
  - Anesthetics
  - Barbiturates
  - Benzodiazepine tranquilizers (Valium[b]; Librium[b]; Dalmane[b]; Serax[c])
  - Ethanol
  - Inhalants (volatile solvents)
  - Marijuana
- Psychiatric drugs
  - Antipsychotics
    - Phenothiazines (Thorazine[d]; Mellaril[e])
    - Butyrophenones (haloperidol)
    - Thioxanthenes (Taractan[b]; Navane[f])
  - Antidepressants
    - Tricyclics
    - MAO inhibitors
- Hallucinogens
  - Lysergic acid diethylamide (LSD)
  - Dimethyltryptamine (DMT)
  - Mescaline
  - Psylocibin
  - Dimethoxyamphetamine (DOM; STP)
  - Phencyclidine (PCP)
  - Cannabinoids (THC, high doses)
- Opiate drugs
  - Heroin
  - Morphine
  - Codeine, oxycodone (Percodan[g])
  - Dihydromorphone (Dilaudid[h])
  - Meperidine (Demerol[i])
  - Propoxyphene (Darvon[j])
  - Pentazozine (Talwin[i])
  - Paregoric
  - Methadone (Dolophine[j])
  - L-alpha-acetyl methadol (LAAM)
  - Illicit synthetic narcotics ("designer drugs")

[a] Boehringer Ingelheim, Ridgefield, CT; [b]Roche Products, Manati, PR; [c]Wyeth Laboratories, Philadelphia, PA; [d]Smith, Kline and French Laboratories, Philadelphia, PA; [e]Sandoz, Inc., East Hanover, NJ; [f]Roerig, New York, NY; [g]DuPont Pharmaceuticals, Wilmington, DE; [h]Knoll Pharmaceutical Co., Whippany, NJ; [i]Winthrop-Breon Laboratories, New York, NY; [j]Eli Lilly and Company, Indianapolis, IN.

changes in libido, sexual dysfunction, and disruption of fertility.

Marijuana

During the past several years, new concerns have arisen over the possibility of adverse effects on the reproductive system from marijuana use. Several studies show changes in reproductive hormone levels that are consistent with the development of infertility and sexual dysfunction. In response to these concerns, new emphasis has been given to the study of marijuana's effects on reproduction, and several significant findings, both in laboratory animals and clinical studies with human subjects, have contributed to our understanding. Although most of these studies show clear changes in reproductive function, there are also conflicting reports and apparent inconsistencies in the findings.

Studies with laboratory animals clearly show that marijuana and Δ^9-tetrahydrocannabinol (THC), the principal psychoactive ingredient, inhibit secretion of the pituitary hormones, LH and FSH, as well as PRL. These changes in pituitary hormone levels produce decreases in sex steroid hormones. Because of its potent antigonadotropic activity, THC inhibits ovulation. However, ovulation can be induced by exogenous gonadotropins or gonadotropin-releasing hormone (GnRH), even in the presence of high concentrations of THC, suggesting that the antiovulatory effect of THC does not occur at the gonadal or pituitary level, but rather at the hypothalamic level.

Most of the reported findings on the effect of marijuana and its main constituents on primate pituitary hormones have been obtained in the rhesus monkey. Acute administration of THC results in marked reductions (50% to 80%) of serum FSH and LH that last up to 24 hours, depending on the dose administered. As in nonprimate animals, the inhibition of gonadotropin levels by THC appears to take place at the level of the hypothalamus, as both LH and FSH are released from the pituitary gland in response to GnRH in monkeys treated with THC, and THC does not interfere with the estrogen-induced LH surge in castrate female monkeys.[3] Acute administration of THC produces marked suppression of PRL levels.[4] The maximal effect is observed between 30 and 90 minutes after drug treatment. It is likely that the psychoactive properties of THC are related to these effects on reproductive hormones, as nonpsychoactive components of marijuana have no effect on these hormones.

Several studies have examined the effects of marijuana and/or THC on the menstrual cycle. At dose levels that elicit blood concentrations of THC similar to those found in regular human marijuana users, THC disrupted the menstrual cycle in the rhesus monkey. When THC was given during the follicular phase, ovulation was inhibited and hormones remained at basal levels throughout the treatment cycle,[5] and when THC was given during the luteal phase, only slight changes were observed in the hormones of the treatment cycle,[6] but in both cases there was a continued disruption following cessation of the drug treatment. Normal ovulation and hormonal concentrations were restored several months after the cessation of THC administration. Simultaneous administration of exogenous gonadotropins during chronic treatment with THC inhibits the drug effect. Ovulation was restored and normal hormone concentrations were observed. These studies further demonstrate that the antiovulatory effect of THC in the nonhuman primate does not occur primarily at the ovarian level.[7] The mechanism for the prolonged disruption of the menstrual cycle after discontinuation of short-term THC treatment is not known. PRL levels, which were markedly elevated during this post-treatment period, may be involved.

Further studies in monkeys examined the effect of continuous THC treatment on the menstrual cycle and the development of tolerance to the drug effects.[8] All monkeys exhibited normal hormone concentrations and ovulation during the control and vehicle treatment cycles, and menstrual cycle lengths were within normal limits of the colony. The monkeys were given THC (2.5 mg/kg or 1.25 mg/kg) three times per week. After the drug injections began, none of the monkeys ovulated or showed normal hormone levels. The duration of the drug effect (days until next normal menstruation) was 135, 110, and 103 days for the monkeys treated with the 2.5 mg/kg dose of THC and 120 and 70 days for the monkeys treated with the 1.25 mg/kg dose. After tolerance to the drug effects developed, normal cycles were re-established. Ovulation was again detected by laparoscopy and normal concentrations of gonadotropins and steroids were observed. Comparisons were made of PRL concentrations during control cycles, during the period of disruption, and after menstrual cycles were restored. There were no significant differences in PRL concentrations. The previously observed elevations in PRL levels following discontinuation of short-term drug treatment were not observed with chronic drug treatment. Since both gonadotropins

and sex steroids were at basal levels during the period of disruption, it is likely that THC inhibited the hypothalamic control of pituitary activity; however, with chronic drug treatment, tolerance develops to this inhibitory effect of THC and normal cycles are re-established. Pharmacokinetic data from this study showed no increase in drug metabolism or clearance that could have produced tolerance. Thus, it is likely that the tolerance that develops to the reproductive effects of THC is due to adaptation of neural mechanisms in the hypothalamus.

These studies in rhesus monkeys are consistent with the clinical studies of young women who regularly use marijuana. Twenty-six women who reported using marijuana at least four times per week were compared with 16 age-matched controls who stated that they had never used marijuana. Marijuana users had shorter menstrual cycles and shorter luteal phases.[9] A recent double-blind study demonstrated the acute suppression of LH concentrations when women smoked marijuana during the luteal phase of the menstrual cycle.[10] These women smoked a single 1-gm marijuana cigarette containing 1.8% THC, and LH concentrations were decreased by 30%. Placebo cigarettes caused no change in LH concentrations. Additional studies indicate the development of tolerance and return to apparently normal hormone concentrations in young women who regularly used marijuana.[11] It is clear now that development of tolerance must be considered as a variable in reproductive studies in young men and women who use marijuana and may help to explain some of the conflicting data in human and laboratory animal studies.

In male laboratory animals, acute or chronic administration of THC results in lower serum concentrations of testosterone (T).[12] In the male rhesus monkey, a single dose of THC causes a significant decrease in blood levels of T as early as 60 minutes after administration; this decrease lasts as long as 24 hours. The decrease in T can be reversed by administration of human chorionic gonadotropin (hCG) (indicating that THC does not directly inhibit testicular synthesis of T) and by GnRH (suggesting a lack of effect at the pituitary gland).[13] Studies with chronically exposed male monkeys show that tolerance develops to the hormonal effects of THC. After tolerance develops, testosterone levels are still decreased by THC treatment, but for shorter periods of time.

Conflicting reports exist on the effects of marijuana on T concentrations in men. Kolodny et al.[14] reported a lowering of plasma T in heavy marijuana users as compared with age-matched controls who had never used marijuana. A later, well-controlled prospective study failed to confirm earlier findings.[15] Studies of hormone levels in marijuana users are hard to interpret. The actual amount of drug that reaches the circulation can be evaluated only by careful measurement of THC levels in the blood. Concentrations of T vary considerably even in normal men, so it is difficult to evaluate the biologic significance of drug-induced changes when they do occur. Other questions remain to be answered, including what role tolerance plays in the effects of THC on hormone levels in men and what are the possible effects of even moderate changes in sex hormones on fertility and sexual function in men.

The effects of marijuana and THC on spermatogenesis has been studied in humans and laboratory animals. Studies in laboratory rodents[16,17] and in dogs[18] have shown that chronic treatment with marijuana or THC can cause decreased testicular size, degenerative changes in spermatogenesis, and abnormal sperm morphology. In vitro studies have shown that cannabinoids inhibit protein and nucleic acid synthesis and glucose metabolism in the rat testes. Inhibition is greatest in the seminiferous tubule cells.[19,20] Inhibition of these processes could account for the decreased sperm production associated with marijuana exposure in animals. Several studies have examined sperm counts and sperm morphology in men who are chronic marijuana users. Kolodny et al.[14] first reported that 6 out of 17 chronic marijuana smokers had sperm counts below 30×10^6/ml. Hembree et al.[21] studied chronic marijuana smokers in a hospital setting. Subjects smoked up to a minimum of ten cigarettes per day (each containing 20 mg of THC) for a 4-week period. Sperm counts were significantly lowered after the treatment period. In a later study, Hembree et al.[22] conducted a similar study in men with an initial sperm count of >100 million and normal sperm motility. As in the previous study, sperm concentrations were significantly lower during the 2 weeks after the 4-week smoking period (motility not studied) and had returned to normal by 3 to 4 weeks after marijuana smoking ceased. In summary, studies in which animals were treated with marijuana or THC are consistent with studies in humans who use marijuana. Both show decreased sperm production following chronic marijuana use. The significance of these observations is unclear, since there are no clinical studies evaluating the effects of

marijuana on infertility in men. It is clear from the current evidence that marijuana use should be considered as a factor that may contribute to unexplained infertility in men.

Cocaine

Cocaine is a CNS stimulant, acting mainly on the catecholamine neurotransmitters. Cocaine acts peripherally to inhibit nerve conduction (local anesthetic) and to prevent norepinephrine uptake at nerve terminals. Increased concentrations of norepinephrine at the nerve terminals causes vasoconstriction and tachycardia with an abrupt rise in blood pressure. Some reports indicate that cocaine may actually heighten sexual powers and sexual arousal temporarily. Cocaine has been applied topically to male and female genitalia to increase sexual performance in human males, probably due to its effect as a local anesthetic, thereby prolonging erection and delaying ejaculation. In addition, many claims that cocaine is an aphrodisiac may be attributed to the fact that, like other CNS drugs, it suppresses inhibitions. The acute effect of cocaine at low to moderate dosages is an increase in LH, whereas at higher doses, cocaine appears to inhibit LH release.[23,24] Therefore, at low to moderate dosages, an increase in T should be expected, and at higher dosages, T levels should be inhibited. Studies in female ovariectomized rats show that moderate doses (10 to 20 mg/kg of cocaine) increase and high doses (40 mg/kg cocaine) decrease serum LH. FSH was unaffected at any dosage, whereas serum PRL levels were decreased by cocaine at either dosage level.[25] The effects of cocaine on LH and PRL appear to be due, in part, to their effect on the neurotransmitters, norepinephrine and dopamine. Cocaine prevents reuptake of released norepinephrine at nerve endings, leading to increased levels of neurotransmitter in the nerve terminals and enhanced effect. Cocaine also has been shown to block the reuptake of dopamine. Inhibition of PRL and stimulation of LH release by cocaine may be due to these actions on neurotransmitters. It is not known whether pharmacologic stimulation of gonadotropin release and inhibition of PRL release can cause disruption of reproductive function in humans. It is likely that chronic cocaine use would result in temporary depletion of hypothalamic neurotransmitters and inhibition of gonadotropins and elevated PRL concentrations; however, no studies on the effects of cocaine on reproductive hormones in humans have been published. This may be because the other life-threatening toxicities of cocaine on other bodily systems and the clear risk of cocaine dependency overshadow the concern about effects on reproductive hormones.

Narcotics

The effects of narcotic drugs on reproductive function have been observed in heroin addicts. Clinical manifestations, such as decreased sexual desire and performance, menstrual irregularities, and infertility among narcotics users are attributed, in part, to altered gonadal functions.[26–28]

Acute doses of morphine have been found to prevent ovulation in laboratory animals,[29] and chronic doses of morphine or heroin totally disrupt the estrous cycle in rodents and the menstrual cycle in women.[26,30] It is clear that the narcotics produce these disruptions in female reproductive function by altering reproductive hormone levels. Significant reductions in both serum LH and FSH have been observed in narcotic-treated female rodents and humans.

Heroin addicts have decreased fertility and atrophy of male accessory sex organs. Similar findings were observed in laboratory animals, with marked decreases in seminal vesicle and prostate weights in narcotic-treated rats. This disruption of male fertility by narcotics appears to be produced by alteration of reproductive endocrine function; however, serum concentrations of FSH and LH in male addicts have been reported as unchanged,[31] significantly decreased,[32] or slightly increased.[33] In rodents, significant decreases in LH levels were observed after administration of morphine.[34]

Studies in the male rhesus monkey described the effect of acute morphine administration on plasma LH and T levels.[35] In these studies, morphine sulfate (0.25 to 1.0 mg/kg) or saline vehicle was given to adult monkeys by an intravenous injection through an indwelling jugular catheter. Significant decreases in LH levels were observed 40 to 100 minutes after drug treatment. LH levels remained below pretreatment levels for at least 140 minutes. Significant depressions in plasma T levels occurred by 80 minutes after morphine administration, and T remained significantly depressed for at least 100 minutes. The decrease in LH levels preceded the depression of circulating T by approximately 40 minutes. This difference in time of drug effect on the hormones corresponds with the typical physiologic lag period between LH changes and subsequent T changes.

The majority of current evidence concerning the opioid-induced decrease in plasma T levels suggests a CNS-mediated action. A lack of a direct testicular effect is supported by studies in monkeys pretreated with hCG to remove the effects of endogenous LH on T production.[35] Morphine administration subsequent to hCG had no direct effect on T levels. Numerous studies indicate that narcotics act via the hypothalamus and not through a direct pituitary effect. GnRH, administered to monkeys after the administration of morphine, produces a LH response that is indistinguishable in magnitude, duration, and time of onset from that observed in monkeys pretreated with vehicle.[36] The absence of a direct pituitary effect of narcotics has been demonstrated further by in vitro studies in which addition of morphine sulfate to an incubation system containing rat anterior pituitary tissue had no effect on gonadotropin release stimulated by GnRH.[37] Thus, it appears that the effects of narcotics on gonadotropin levels are elicited at a level above the pituitary, probably involving modulation of the endogenous opioid peptides (EOP). Studies have been done using the EOP and opioid drugs to evaluate the interaction of EOP with reproductive endocrine function. Administration of the Leu-enkephalin analog D-Ala^2,D-Leu^5-enkephalin to male monkeys decreased both T and LH levels.[36] This decrease in LH concentration is consistent with decreases observed in normal human males administered a Met-enkephalin analog.[38] In contrast, no statistically significant alterations in plasma LH levels were observed in male monkeys administered a 10.0-mg/kg dose of beta-endorphin; however, studies in human male volunteers administered a 40 mg/kg dose of beta-endorphin showed a decrease in serum LH.[39] When compared on a relative basis, the pharmacologic effects of morphine and various EOP may be used to infer differential actions on these various narcotic receptor subtypes. Morphine has been shown to have greatest selectivity for mu receptors; D-Ala,^{2} D-Leu^5-enkephalin is delta-selective; and beta-endorphin has about equal actions upon mu and delta receptors. When compared on a molar basis, these findings suggest that the receptor subtypes responsible for opioid-induced inhibition of plasma LH are delta. Further studies have been done using the opiate receptor antagonist, naloxone. Naloxone administration produces increases in plasma LH levels, presumably by blocking the tonic inhibitory effects of the EOP. This effect has been demonstrated with naloxone administration in humans,[40,41] monkeys,[36] and rats.[42] When administered to monkeys after pretreatment with opioids, naloxone completely reversed the opioid effects and produced increases in plasma LH levels that did not differ significantly from those seen with naloxone alone. These results indicate that naloxone can reverse the tonic inhibitory effect of the EOP on gonadotropin secretion and that this effect is mediated through opiate receptors. The precise mechanism by which opioids modulate neuroendocrine function is unknown. The most likely mechanism would appear to involve one of the various putative synaptic transmitters that regulate hypothalamic endocrine neurons.[43–45]

Alcohol

Alcohol is another example of a commonly abused drug that affects the reproductive system. Its effects on reproduction have been studied primarily in male subjects. In a study of 16 normal men, LH and T levels were determined during a period of acute alcohol intoxication.[46] Careful monitoring of both T and LH levels demonstrated that the primary effect of alcohol is on the testicular synthesis and secretion of T. Both ethanol and its major metabolite, acetaldehyde, inhibit the testicular enzymes involved in T synthesis.[47] This testicular effect of alcohol is worsened by the increased metabolic clearance rate of T by the liver, which also is caused by acute alcohol consumption.[48] As expected, male alcoholics and animals treated chronically with alcohol produce less T and have lower serum T levels.[49,50] Multiple endocrine abnormalities are seen in men with alcoholic cirrhosis. Hypogonadism and gynecomastia are common manifestations of alcoholic cirrhosis in men. These manifestations emphasize how important normal liver function is to the maintenance of reproductive function. With destructive liver disease, the pattern of circulating sex steroids changes. Increased levels of estrogenic steroids are observed in these men. These estrogenic steroids secondarily suppress gonadotropins and T production and inhibit the functioning of accessory sex glands.[49]

Thus, the primary toxic effect of alcohol appears to be testicular.[51] Reduction in circulating T concentrations and decreased responsiveness to exogenous hCG are consistent with Leydig cell damage. This does not preclude inhibition of hypothalamic-pituitary function as being involved in alcohol-related effects. LH concentrations tend to be normal in alcoholics instead of being elevated as might be expected, and there is good evidence of a dual effect

on gonadal and hypothalamic-pituitary function in men with alcoholic liver disease.[52]

Alcohol can directly inhibit penile tumescence and ejaculatory capability through a direct action on spinal reflex centers.[53,54] In alcoholic and nonalcoholic men, a blood alcohol level of 40 to 50 mg/dl inhibits penile tumescence, and with a blood alcohol level of above 100 mg/dl, penile tumescence is almost completely inhibited. Chronic alcoholism may result in permanent impotence in men, even after years of sobriety.[55]

Both acute and chronic alcohol exposure can cause abnormal spermatozoa. After acute alcohol consumption (0.4 to 0.8 gm/kg), sperm samples from a group of men revealed spermatozoa with heads broken off, tails curled, and distended midsections.[56] Sperm specimens from alcoholic men able to produce an ejaculate were grossly abnormal with fewer total cells and many abnormal cells.[50]

A few studies have examined the effects of alcohol on reproductive hormones in the female. Alcohol does appear to inhibit gonadal activities in female rodents.[57,58] These effects may not be as pronounced in women and laboratory primates. In clinical studies, there was no significant effect of acute alcohol ingestion on either sex steroids or gonadotropins.[59] A similar lack of effect was observed in female rhesus monkeys when alcohol was administered at various phases of the menstrual cycle.[60] These results demonstrate that women and female nonhuman primates may be less sensitive to the acute gonadal effects of alcohol, although females may not be less vulnerable to the toxic effects of chronic alcohol use on reproductive endocrinology. Chronic use of alcohol and alcoholism have been related to infertility[61,62] and menstrual disorders in women,[63,64] and disruption of reproductive function has been shown with alcohol self-administration in female monkeys.[65]

Other Central Nervous System Drugs

The barbiturates are classified pharmacologically as sedative-hypnotic agents. They are general depressant drugs, and the CNS has a particular sensitivity to this effect. Although the exact mechanism of action is not known, barbiturates are known to depress neural activity in various brain regions. Their potent depressant effects have made them popular as drugs of abuse, both for their sedative effects and for the effect they produce in combination with other drugs of abuse. Barbiturates have been used as anesthetic agents in reproductive studies in laboratory animals for many years. These studies provided the description of the inhibitory effects of these drugs on reproductive hormones, observations that resulted in the use of these drugs as important tools in the study of reproductive function. Most of these investigations concerned the neuroendocrine control of female reproductive cycles, but some information is available on the effects of barbiturates in male animals.

The general effect of barbiturates is an inhibition of both LH and FSH, with subsequent depression of steroid hormone secretion. Barbiturate anesthesia blocked both spontaneous and steroid-induced LH release in rats[66] and hamsters.[67] In these animals, the spontaneous release of LH is controlled by the light-dark cycle and occurs at a specific hour and day of the estrous cycle. Prolonged barbiturate anesthesia did not block the steroid-induced LH surge in rhesus monkeys.[68] This suggests that barbiturates act on neural elements—in the medial preoptic area—that generate the circadian stimulus mediating LH release and not at the medial basal hypothalamus, where steroid hormones have their action. The effect of barbiturate anesthesia in male animals is similar to the effect in females. Phenobarbital inhibits gonadotropin secretion and blocks the rise in serum gonadotropin levels that normally follows castration.[69] Both of these effects can be reversed by the administration of GnRH. LH secretion and ovulation can be restored in barbiturate-treated animals by infusion of GnRH, indicating a hypothalamic site of action for the barbiturates.[70] Studies in both male and female animals showed that barbiturate pretreatment can even potentiate the effect of GnRH on LH release.[69,71]

The effect of barbiturates on PRL concentrations is less well established. Nonspecific stresses, such as anesthesia and blood drawing, increase PRL release. Studies employing these techniques in the evaluation of PRL concentrations are difficult to interpret. Acute administration of barbiturates in relatively small doses appears to cause the release of PRL.[72,73] However, barbiturate anesthesia blocks the release of PRL caused by ether or estrogen administration.[74]

An additionally well-recognized effect of the barbiturates is stimulation of hepatic mixed-function oxidases. The same enzyme systems are involved in the metabolism of the steroid hormones. Thus, the barbiturates have the potential for disrupting reproductive hormones by several mechanisms. Such effects have not, however, been demonstrated in clinical studies.

Phencyclidine hydrochloride (PCP) was one of a group of related drugs developed as anesthetic agents and animal tranquilizers. PCP is now a frequently abused drug commonly referred to as "angel dust." It has been classified as a schedule I controlled substance, and legal manufacture and sale of the drug was discontinued in 1978.

Many areas of the brain are affected by PCP. It has been shown to alter the catabolism, steady state levels and turnover rates of a number of neurotransmitters in the CNS, and current evidence indicates that the effects of PCP are caused by alterations in the function of several neurotransmitters. There have been several investigations of the effect of PCP and ketamine (a PCP analog) on reproductive hormones. Ferin et al.[75] showed that release of LH, growth hormone, and PRL persisted under prolonged sedation with PCP, but the secretion of PRL in response to the administration of thyrotropin-releasing hormone (TRH) was increased in animals under sedation. Zaidi et al.[76] reported that serum T levels and production rates were not significantly different in conscious or ketamine-anesthetized male rhesus monkeys. Numerous endocrine studies in laboratory primates have used PCP or ketamine as an anesthetic agent for minor surgical and blood-drawing procedures because these agents have less effect on reproductive hormones than do other anesthetic agents.

Another study examined the acute and chronic effects of PCP on reproductive hormone levels in male rats. Acute administration of PCP at recreational dosage levels produced only a slight depression of serum T and LH levels. However, both hormones were strongly reduced after nine daily treatments, and after discontinuation of drug treatment, both hormones were significantly elevated above control levels and returned to normal value by 60 days. A similar period of elevated serum T and LH was found in adult male rats that received nine daily injections of PCP during sexual maturation. The magnitude of the increased hormone levels in the PCP-treated juvenile rats was several times that of the rats that received the drug as adults, and the period of elevation persisted for 80 days.[77] It is not known whether PCP inhibits reproductive hormones in humans.

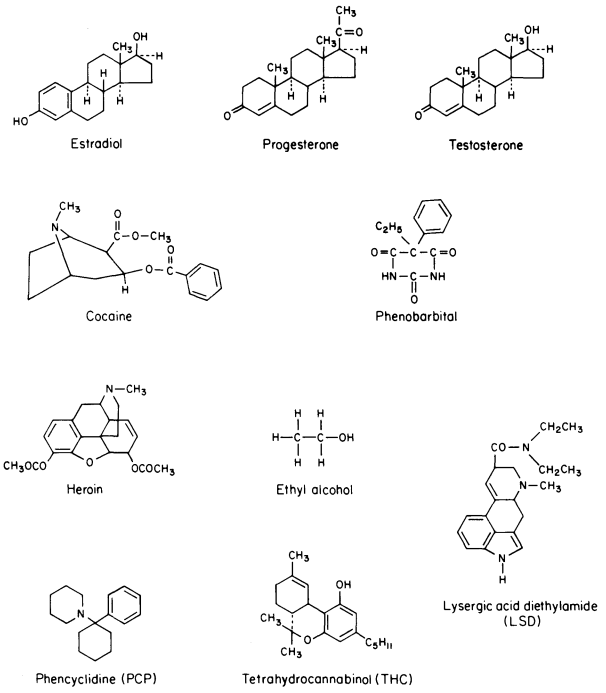

Figure 1 Representative chemical structures of the drugs of abuse and steroid reproductive hormones.

Summary

It is clear that a number of CNS agents, including drugs of abuse, can inhibit reproductive function. Figure 1 shows the chemical diversity of some of the drug groups that affect reproductive hormones. Their structural dissimilarity to the steroid hormones is also readily apparent in the figure. These chemically diverse drugs share an important pharmacologic property: they are highly potent neuroactive drugs, and they can disrupt hypothalamic-pituitary function. Although it is frequently difficult to distinguish between direct drug actions on the hypothalamic-pituitary axis and subsequent effects on gonadal hormones and sex accessory gland function, the distinction is an important one. Most neuroactive drugs produce only transient effects on the central nervous pathways necessary for normal gonadotropin secretion. The disruptive effects of these drugs are likely to be transient and completely reversible, and tolerance to the inhibitory drug effects may occur even with continued drug use. Under these circumstances, normal adults may experience only subtle changes in sexual function. However, individuals with compromised reproductive function may exhibit major problems. It is also likely that adolescents may be at substantial risk for reproductive damage from these neuroactive drugs since the endocrine events associated with puberty are dependent on the normal development of the hypothalamic-pituitary axis.

DRUG ABUSE EFFECTS ON PREGNANCY AND FETAL/PERINATAL DEVELOPMENT

It is well recognized that drugs taken during pregnancy can produce devastating effects on fetal development. Dysmorphic teratology is considered to be the major risk associated with drug use in pregnancy, but additional concern is behavioral teratology. Behavioral effects are less obvious and, therefore, not as easily recognized as dysmorphic effects. Although most drugs of abuse do not produce obvious congenital malformations, there is increasing evidence of neurologic and behavioral effects that can impair a child's development. Recent developments in the methods used to evaluate neonatal behavior and neurologic development are providing a better understanding of behavioral teratology.

The maternal-placental-fetal unit is a complex pharmacologic model. Each component is an independent and dependent contributor to the overall picture of drug disposition and toxicity. Additionally, the pharmacologic and physicochemical properties of the drug(s) or its metabolites can play an important role in the development of teratologic effects. Drug abuse frequently represents an optimal combination of the factors favoring adverse effects on pregnancy (Table 3). The drugs produce potent and reinforcing CNS effects on the pregnant mother. She is likely to use them frequently and throughout pregnancy. The highly potent CNS drugs that readily cross the blood–brain barrier (lipid-soluble; low molecular weight) also readily cross the placenta. The preferred routes of administration (intravenous or inhalation) produce high serum concentrations that may not undergo first-pass metabolism and may cross the placenta in large quantities. The illicit drugs of abuse are readily available, but they are expensive and frequently contain toxic contaminants. Most drugs of abuse have pharmacologic actions that are undesirable in pregnancy, apart from their direct fetotoxic actions. Both stimulants and depressant drugs can decrease appetite and result in inadequate nutrition during pregnancy, and the cardiovascular effects of the drugs can hinder placental circulation and placental metabolic function. At birth, the drugs can persist in fetal circulation and interfere with neonatal adaptation. Most of the drugs of abuse have no specific antagonist for neonatal resuscitation and certain drugs cause a newborn abstinence syndrome. Maternal drug abuse that continues after the pregnancy can result in continued drug exposure of the infant during nursing and disruption of infant care.

Table 3 Teratogenic Potential of Drug Abuse

Maternal factors
Amount and duration of drug use
Poly-drug abuse
Routes of administration of drugs
Altered pharmacokinetics in pregnancy
Prenatal medical care
Parenting abilities
Placental factors
Placental transfer of drugs
Placental metabolism of drugs
Direct placental toxicity of drugs
(e.g., effects on placental growth and development and effects on placental circulation)
Fetal factors
Genetic susceptibility to drug toxicity
Stage of embryonic/fetal development
Immaturity of drug biotransformation activities
Drug factors
Pharmacologic actions
Potency
Contaminants in illicit drugs

Since drug abuse has such a potential for harmful effects on pregnancy, it is perhaps surprising that the associations are not well documented in the clinical literature. There are several reasons why this is not the case. Drug and alcohol dependency in pregnancy has been described as one of the most frequently missed diagnoses in obstetrics. This situation could be significantly improved with routine urine toxicology during prenatal visits. Excellent guidelines recently have been published for the recognition, management, and/or referral to treatment facilities for drug dependence in pregnancy.[78] Even the research on drug abuse in pregnancy reflects a somewhat ambivalent approach to the problem. Many of the studies are retrospective, based on the recall of the pregnant woman during or after the pregnancy. Prospective studies are complicated by the intervention strategies that attempt to persuade women to discontinue or modify their drug use to minimize the risk to the pregnancy and unborn child. Statistical interpretation of all of the studies is overwhelmed by the presence in the subjects and controls of other serious risk factors, so we may never learn the independent risk of drug abuse in pregnancy. The studies are further complicated by the inability to perform the types of research on the fetus that might yield data on drug effects on human development. Despite the limitations of such studies, there are some useful observations that show the risks of drug abuse during pregnancy.

Effects on Pregnancy Hormones and Length of Gestation

There is convincing evidence that the neuroactive drugs of abuse can inhibit both gonadotropins and sex steroids during the menstrual cycle. It is reasonable to presume that similar inhibitory effects on chorionic gonadotropins and sex steroids may occur if these drugs are used during pregnancy. Inhibition of pregnancy hormones could result in a range of toxicities from insufficient placental growth and function to pregnancy termination. In order to determine whether such toxicities are produced through a disruption of the endocrine function of the placenta, careful endocrine studies must be done throughout the course of the pregnancy and in close proximity to the episodes of drug use. Such studies are difficult to accomplish, particularly with the illicit drugs. There are, however, several studies that indicate that disruption of pregnancy hormones may be partly responsible for some of the problems when marijuana is used during pregnancy.

The extent of marijuana use by pregnant women is thought to be comparable to the estimated 14% of women (ages 18 to 25) who use marijuana in the general population. This is sufficient to represent a serious health hazard if marijuana is found to have a deleterious effect on pregnancy or fetal growth and development. Several studies have presented evidence linking certain maternal and fetal risk factors with marijuana use during pregnancy. A prospective study examined women who reported use of marijuana before and/or during pregnancy.[79] Infants born to heavy users showed significantly more symptoms of CNS immaturity (inability to self-quiet, heightening of tremors and startles, failure to react to visual stimuli). A recent study examined the effect of marijuana use during pregnancy on length of gestation and infant birth weight.[80] Compared to nonuse, an average use of marijuana six or more times per week during pregnancy was associated with a significant reduction in the length of gestation after consideration of the effects of nicotine, alcohol, parity, prepregnancy weight, and sex of the infant. Among heavy marijuana users, the effect on gestation length was dose-dependent.

An examination of labor and delivery of mothers who had used marijuana during pregnancy demonstrated an increased incidence of meconium in the amniotic fluid in the newborn infants. Need for neonatal resuscitation was also greater, particularly when the mother had used marijuana close to delivery.[81] When Hingson and associates examined the effects of using marijuana, alcohol, or both during pregnancy, they found a relationship between maternal marijuana smoking and poor fetal development.[82] Women who used marijuana during pregnancy delivered infants with significantly decreased birth weight, body length, and head circumference, and these infants were five times more likely to have dysmorphic features usually associated with fetal alcohol syndrome.

The effect of THC, the principal psychoactive component in marijuana, has been studied in pregnant rhesus monkeys.[83] The THC or vehicle was administered during different periods of gestation and effects on pregnancy outcome and hormone concentrations during pregnancy were studied. The most obvious effects were observed when THC was administered from early in the pregnancy. Three of the five pregnancies were aborted within days after the drug injections began; one pregnancy resulted in stillbirth at term; and one pregnancy resulted in the birth of an infant of normal size and appearance. The three abortions were associated with a premature decrease in chorionic gonadotropin and progesterone (P) concentrations. Estradiol (E_2) concentrations were significantly higher than in vehicle control pregnancies in the two pregnancies that continued until term. Daily THC administration during the middle or third portions of gestation resulted in less pregnancy loss (one premature birth and four live births at term with THC treatment during the middle portion; two premature births and three live births at term with THC treatment during the third portion of gestation). All of the premature infants died within 2 weeks of birth of the complications of prematurity. The weights of the infants at birth and weaning were not significantly different for the full-term infants of vehicle control pregnancies and full-term infants that were exposed to THC during gestation. Since no effects on intrauterine growth and development were detected (by ultrasound) in the drug-treated pregnancies, the most likely cause of the early pregnancy loss was disruption of placental endocrine function.

There is evidence that a LH-releasing hormone-like hormone of placental origin controls the secretion of chorionic gonadotropin in human and nonhuman primates.[84] It is reasonable to postulate that the inhibitory effects of THC on placental function early in pregnancy are due to an effect on the placental LH-releasing hormone-like sub-

stance in a manner similar to its effect on hypothalamic LH-releasing hormone. If, in the monkey studies, the THC administration began after the physiologic decline in macaque chorionic gonadotropin (mCG), no effect on P concentrations was observed, and no effect on mCG or P concentrations was observed during the remainder of the pregnancy. The implication is that there is a critical interval for the inhibition of mCG by THC administration. This fact may explain why Braunstein et al.[85] observed no significant differences in hCG concentrations or outcomes of pregnancy in women who used marijuana during pregnancy and those who did not.

Effects on Fetal Growth, Development, and Malformations: The Fetal Alcohol Syndrome

Fetal alcohol syndrome (FAS) was first recognized as a syndrome in 1973.[86,87] Unlike other problems associated with drug abuse in pregnancy, FAS is a clinically observable entity with specific parameters for diagnosis. Three parameters make up the primary presentation of FAS: (1) prenatal growth deficiency in length and weight; (2) microcephaly; and (3) short palpebral fissures. Infants with FAS are small for their gestational age and, unlike other small infants, they remain small for their age through childhood.

A prospective study of over 800 women examined the effect of maternal drinking during pregnancy using regression analysis, which adjusted for such factors as smoking, maternal height, maternal age and parity, gestational age, and sex of the child. This study found that, for each ounce of alcohol consumed per day during late pregnancy, there was a resultant depression in birth weight of 160 gm.[88] Numerous studies have confirmed alcohol use during pregnancy as a risk factor for intrauterine growth retardation.[2,89,90] There also is the possibility that drinking prior to pregnancy may have residual effects on subsequent prenatal growth. Little et al.[91] found that birth weights of children born to alcoholic women who abstained during pregnancy were about 260 gm below those infants of nonalcoholic women, and the average birth weights for infants of alcoholic women who drank during pregnancy was about 490 gm below normal. Other risk factors related to alcohol use during pregnancy may contribute to the decreased birth weight. In one study, maternal smoking was found to have an additive effect to that of alcohol.[2] Alcohol abuse alone resulted in a 2.4-fold increase in intrauterine growth retardation, smoking had a 1.8-fold increase, and the combination of alcohol abuse and smoking was associated with a 3.9-fold increase. Since chronic alcoholics tend to be undernourished, it is possible that growth deficiency in FAS may be due, in part, to alcohol-related nutritional deficiencies.[92] Alcohol impairs absorption and metabolism of nutrients, vitamins, and minerals.[93] Although animal studies that use "pair-feeding" techniques minimize the importance of altered nutrition in the production of FAS,[94] alcohol-related inhibition of transport across membranes may be important in the nutritional contribution to FAS.[95] Thus, altered nutrition cannot be ruled out as an indirect factor in FAS. Other alcohol-related illnesses, socioeconomic conditions, and related stresses also may contribute to the toxic effects of alcohol abuse. However, unlike infants of the women in many of the drug-abuse studies, infants of alcoholic women who come from mostly Caucasian, middle socioeconomic backgrounds clearly demonstrate the manifestations of FAS.[88]

It was the similarity of the facial features associated with FAS that first drew clinical attention to the syndrome. Clarren and Smith[96] noted that the key facial features are short palpebral fissures, hypoplastic upper lip with thinned vermilion, a diminished-to-absent philthrum, and, frequently, midfacial and mandibular growth deficiency. The facial features of FAS are thought to result from midfacial hypoplasia. Studies in an animal model have shown that facial features similar to FAS can be produced in mice when exposure occurs during the gastrulation stage of embryogenesis.[97] Other anomalies include cardiac septal defects,[98] skeletal defects,[99] urogenital defects,[100] and structural and developmental anomalies of the brain and spinal cord.[101] Behavioral teratology is another remarkable feature of the FAS. There is good evidence that children born to alcoholics are at risk for various behavioral problems, the most serious of which is mental retardation. Studies in laboratory animals demonstrate deficits in learning/memory function with prenatal exposure to alcohol.[102,103]

FAS represents a spectrum of anomalies that are manifest to a different extent in different individuals. The full FAS is seen only in some of the infants of chronic alcoholic women. Other infants of alcoholic mothers have few or none of the fetal alcohol affects. A recent study discovered one difference in alcoholic women whose infants had FAS and those who did not. Women who gave birth to

infants with FAS had lower E_2 and estriol concentrations throughout pregnancy and tended to have lower P concentrations than those alcoholic women whose infants did not have FAS. PRL levels were elevated in all alcoholic women, and hCG concentrations were not different in alcoholic women and abstinent women.[104]

The actual mechanisms by which alcohol produces the effects of fetal alcohol exposure are unknown. The mechanism by which alcohol produces the growth-retarding effect may be different from the mechanism that produces congenital abnormalities. Since there are no clear relationships between quantity of alcohol used during pregnancy and the severity of the FAS, it is reasonable to presume that factors such as maximum blood alcohol concentrations, stage of gestational development, adequacy of nutrition before and during pregnancy, smoking, and other drug use in pregnancy contribute to the severity of FAS. Attempts have been made to establish a safe level of alcohol use in pregnancy, but with so many uncertainties, such information is speculative. In 1981, the Surgeon General of the United States recommended that women abstain from alcohol throughout pregnancy.

Complications of Pregnancy and Labor/Delivery

Heroin addiction was once the only major drug abuse concern in the treatment of pregnant patients. At the present time, cocaine addiction (either alone or in combination with alcohol and/or tranquilizers) is a major drug abuse problem. An estimated 10 million Americans have used cocaine at least once and 5 million use it on a regular basis.[105] The factors that have contributed to this are thought to be the ready availability of cocaine, the ease of administration of cocaine, and the drug's popularity among prominent individuals. Cocaine is recognized as a particularly attractive drug to women as their first drug of abuse.

Significant complications in pregnancy and adverse effects on infants have been reported in women who use cocaine during pregnancy. The use of cocaine during the first trimester of pregnancy was associated with an increased rate of spontaneous abortion and third trimester cocaine use increased the risk of abruptio placentae within 30 minutes of use.[106] It is likely that the increased rate of spontaneous abortion caused by cocaine in early pregnancy is due to decreased blood flow to the fetus as a result of placental vasoconstriction and an increase in uterine contractility caused by increased norepinephrine concentrations. Women who used cocaine in the third trimester reported feeling contractions and increased fetal activity within minutes of cocaine use. The hypertension and placental vasoconstriction in these women caused by cocaine is thought to increase their risk of abruptio placentae. Maternal cocaine use also may cause fetal tachycardia and hypertension. One recent report of perinatal cerebral infarction was thought to be caused by use of a large amount of cocaine by the mother before delivery.[107] Another study of eight newborns who were positive on urine toxicology screening for cocaine demonstrated no potentially life-threatening symptoms at birth.[108]

Impairment of newborn interactive behavior and poor organizational response to environmental stimuli has been demonstrated in infants of women who use cocaine during pregnancy.[107] Similar neurobehavioral impairments have been shown to result from prenatal drug exposure to opiate drugs[109] and to PCP.[110] A recent study demonstrated abnormal sleeping ventilatory patterns in infants of mothers who abused cocaine and PCP during pregnancy.[111] These abnormalities have been implicated as a risk factor for sudden infant death syndrome (SIDS). Infants born to mothers who abuse opiates during pregnancy have a 5- to 10-fold increased risk of dying from SIDS,[112] so the abnormal sleep ventilatory patterns in infants exposed in utero to cocaine and PCP mean that these infants may carry an increased risk of SIDS.

Neonatal Complications

The narcotic abstinence syndrome in newborns is the best-documented neonatal complication of drug abuse in pregnancy. The syndrome consists of a wide variety of features that mimic aspects of the adult narcotic abstinence syndrome. Most significant for the neonate are tremors, high-pitched cry, sweating, exoriation of the extremities, and gastrointestinal upset.[113] Most of the infants of heroin- or methadone-addicted mothers will undergo some degree of withdrawal within hours to days after birth. The incidence of withdrawal may be related to the degree of maternal addiction but not to the severity of the withdrawal symptoms.[114] The severity of the withdrawal symptoms appears to be more related to the degree of poly-drug abuse by the mother and the maternal dosage of methadone.[115]

Infants delivered to mothers who abuse heroin have a higher incidence of perinatal morbidity and mortality than do infants in the general popula-

tion. It has been well established that infants born to heroin-addicted mothers have low birth weights (half below 2500 gm) and are small for gestational age.[116-118] There is evidence that this is due to both prematurity and intrauterine growth retardation. Narcotic drug exposure during pregnancy produces growth delays that are not related to inadequate maternal nutrition or prenatal care[119] and that result from a subnormal number of cells in all organs of the developing fetus.[120] Infants born to mothers on methadone maintenance weigh more at birth than the infants of mothers using heroin, so the usual procedure is to initiate methadone replacement early in the pregnancy.[113,121] Methadone maintenance during pregnancy is, at best, a trade-off. Although the intrauterine stress of narcotics abstinence syndrome is avoided, the newborns suffer a greater postnatal weight loss[122,123] and have a higher incidence of withdrawal and more severe withdrawal symptoms than do the newborns of heroin-addicted mothers.[113] There is evidence that heroin may accelerate lung and liver maturation,[124] which would be helpful in premature birth.

Other perinatal complications of narcotic addiction that have been reported include a higher incidence of meconium staining and perinatal asphyxia and neonatal death following narcotic withdrawal in the last trimester of pregnancy.[120,125] Some studies have found a high incidence of respiratory distress in the neonates,[115,126] and there are reports of an increased incidence of SIDS among infants of women addicted to the narcotic drugs.[111]

Behavioral symptoms that continue through infancy in these drug-exposed infants include irritability, hyperactivity, and feeding and sleep disturbances. Psychological and educational problems may continue throughout early and middle childhood, but the available studies are insufficient to permit definitive conclusions.[127]

Polydrug Abuse in Pregnancy

A significant problem in drug abuse research in pregnancy is lack of control over polydrug use. The prevalence of polydrug abuse among pregnant women who use drugs makes it complex, if not impossible, to determine the effect of abuse of a single drug. The concurrent use of alcohol, stimulants, tranquilizers, PCP, and combinations including sedative/stimulant and pentazocine/tripelennamine (so-called Ts and blues), is common in women who use drugs during pregnancy. In one program, the Perinatal Services Project of Northwestern University, specialized prenatal care for these women results in successful drug abstinence throughout the remainder of the pregnancy of only about 20%. However, with close supervision of nutritional intake in women enrolled in this special program, there was no significant reduction in fetal growth parameters. Intrauterine exposure to the nonopiate drugs and combinations did not reduce birth weight, length, and head circumference as compared with non-drug-exposed infants.[128] The newborn infants exposed to drugs, however, showed significant impairment of their interactive abilities, motor maturity, and organizational responses to environmental stimuli. They were more tremulous and irritable than the control infants and showed significant and unpredictable emotional responses. These studies demonstrated the beginning of the cycle of poor infant responsiveness and maternal rejection: a behavioral pattern that must be interrupted if the mother/infant relationship is to be established. Among the polydrug abuse problems, the use of PCP is of particular concern. PCP has been shown to cross the placenta in both animals and humans.[129,130] The use of PCP during pregnancy has adverse effects on the newborn. A withdrawal syndrome in two infants exposed prenatally to PCP has been reported.[131] PCP-exposed infants were particularly labile and showed marked deficits in their responses to mothering attempts by caretakers.[132]

A 2-year follow-up of the drug-exposed and control infants demonstrated a downward trend in developmental scores, but all of the infants were from a low socioeconomic population, a factor known to adversely affect developmental scores. There has been no long-term follow-up of children who have been exposed to multiple-drug abuse before birth, so their prognosis for emotional and educational development remains unknown. Infants and children of women who use drugs during pregnancy remain at increased risk for various problems, including SIDS,[110] increased rate of infections, including acquired immunodeficiency syndrome (AIDS),[133] and a high rate of child abuse.[134]

DRUG ABUSE AND ADOLESCENT REPRODUCTIVE DEVELOPMENT

Surveys indicate that young Americans have been gradually moderating their use of illicit drugs in recent years; however, adolescent drug abuse is still acknowledged as a national problem. The age of first use of virtually all drugs has steadily de-

clined; and, while the strength of many street drugs has increased, their cost has sharply decreased, increasing their availability to younger buyers. The 1985 National Household Survey found that 1 in 5 (22%) of 12- to 17-year-olds has used marijuana. About half of those who have ever used marijuana have continued to use it (i.e., had used it in the month preceding the survey).[1] Typically, persons who have a degree of experience with marijuana (used it more than ten times) will become involved in the use of another illicit drug and those who use illicit drugs other than marijuana are likely to continue using at least three substances concurrently.[135] By the time they are high school seniors, the majority of adolescents have tried alcohol, tobacco, and marijuana, and 1 in 20 uses alcohol or marijuana daily.[136]

Since adolescence is a critical developmental period of life, heavy drug use and involvement in a drug lifestyle have a greater negative impact than they do in adults. Research shows that adolescents use drugs because they are readily available; they provide a quick, easy, cheap way to feel good; they offer a means of gaining peer acceptance. They may also help modify unpleasant feelings, reduce disturbing emotions, alleviate depression, reduce tension, and help cope with life pressures.[137] Some adolescents (as many as 5% of teens aged 14 to 18 years) have serious drug-related problems and need treatment. These youngsters are generally compulsive, dedicated users with serious personal problems who rely on drugs as self-medication to cope with their problems.[138,139]

The physiologic events associated with normal adolescent development rely on the maturation of the hypothalamic centers that control the release of GnRH. The earliest indication that this process is beginning is an increase in episodic secretion of GnRH and gonadotropins; throughout the course of adolescent development, the secretion of GnRH is of paramount importance. There is evidence that most of the drugs of abuse can interfere with the secretion of GnRH. Inhibition of GnRH during adolescent development is physiologically more significant than inhibition of GnRH in an adult. Thus, drug abuse by adolescents may result in delayed or arrested reproductive development. It is difficult to predict the magnitude of such disruption, but it is reasonable to presume that the developing system is particularly sensitive to pharmacologic inhibition of GnRH. It would also be difficult to identify drug-related disruption of adolescent development without careful evaluation because there is considerable age variation and irregular progress in the normal developmental process. In addition to the risks of long-term disruption of reproductive function, the emotional trauma of arrested sexual development may contribute to the drug-seeking behavior.

The effect of THC or marijuana administration on aspects of pubertal development has been studied in laboratory rodents.[140–142] Treatment with THC lowers plasma LH and T concentrations in male mice and inhibits prostate growth. Interference with testicular development was shown in rats treated daily during puberty with THC,[143] and chronic administration of cannabis extract has been shown to suppress spermatogenesis in rodents.[144,145] Alterations in sexual behavior also has been observed in rats treated early in life or in adulthood with various cannabis derivatives.[146] In prepubertal, female rats, daily THC administration caused a 5-day delay in sexual maturation.[147] These studies indicate that THC and other cannabis derivatives have effects on sexual development in nonprimate species. No clinical studies or studies of drug effects in primates have been done. Concerns have been expressed in the pediatric literature over cases of arrested pubertal development associated with marijuana use,[148] but there are no definitive answers.

Age-dependent effects of the opiate drugs on gonadotropin secretion in rodents have led to the speculation that changes in the activity of the endogenous opioid system might be part of the physiologic mechanism for the initiation of increased GnRH secretion and onset of pubertal development.[149] Since T and LH concentrations have been shown to be significantly depressed in current heroin users, it is reasonable to predict that heroin use might cause a disruption in pubertal development. The one study that has examined hormone concentrations and psychosocial development in young men after chronic heroin use found no significant impairment of reproductive development.[150] It is likely that tolerance develops to the inhibitory effect of the opiate drugs on neuroendocrine function in both adolescence and adulthood.

The impact of drug abuse on adolescent reproductive development has not been researched adequately. In 1981, the Institute of Medicine's report on Marijuana and Health recognized the lack of information on drug abuse effects on adolescent development as an area of particular concern and emphasized the need for new information about the possible adverse effects of marijuana use on the

developing reproductive system.[151] Five years after the publication of the Institute of Medicine's report, this critical issue remains largely uninvestigated.

CONCLUSION

It is clear that drug abuse has the potential for disrupting reproductive function. This is especially true since young men and women of reproductive age are the segment of the population most heavily involved in drug abuse. There is convincing evidence that the drugs of abuse can disrupt neuroendocrine and gonadal function with sufficient magnitude to cause infertility and sexual dysfunction. There is some documentation of such effects in the clinical literature. As a result, most protocols for the evaluation of unexplained infertility now include investigation of drug abuse history as a possible cause of hormonal problems,[152] drug abuse is now recognized as a possible cause of delayed or arrested pubertal development,[153] and the problems of drug abuse and dependency in pregnancy are being recognized and programs are being developed to minimize the risks to mother and baby.[71,121]

There are still many unanswered questions. To what extent does drug abuse contribute to unexplained infertility? Are the effects always reversible if drug use is discontinued? Does disruption of reproductive development (real or perceived) contribute to the drug-seeking behavior of adolescents? What are the medical-legal issues of drug abuse in pregnancy? The research on the reproductive consequences of drug abuse must be given a high priority by the funding agencies if these questions are to be answered. Since it appears unlikely that our drug abuse problems will be solved in the immediate future, the issue of the risks to reproductive function cannot be ignored.

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