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Reproductive risks of cocaine

Botros Rizk[1], Jana L.Atterbury[2] and Lynn J.Groome[2]

Divisions of [1]Reproductive Endocrinology and [2]Maternal–Fetal Medicine, Department of Obstetrics and Gynecology, University of South Alabama, Mobile, AL 36617, USA

TABLE OF CONTENTS

Cocaine use during pregnancy in the USA has increased dramatically in the past decade, and has resulted in an associated increase in a variety of maternal and perinatal complications. However, a number of confounding factors make it difficult to determine the direct impact of perinatal cocaine use on maternal and fetal outcome. Many substance-abusing women use multiple drugs while pregnant, receive inadequate prenatal care and are predisposed to other health problems that impact on perinatal outcome. As a result of the rapid clearance of cocaine and limitations of available screening methods, the identification of individual users can be difficult. Furthermore, the determination of accurate prevalence rates of cocaine use during pregnancy has been frustrated by sampling bias. Cocaine has profound systemic and cardiovascular effects in both the mother and the fetus, and as a result a number of complications (i.e. fetal malformations, preterm labour, placental abruption) have been attributed to perinatal cocaine exposure. In addition, maternal cocaine use has been associated with a number of neonatal abnormalities, including cardiopulmonary effects, somatic changes and neurobehavioural sequelae. It is estimated that US $500 million dollars in additional health expenditure resulted from increased neonatal hospital costs and longer lengths of stay for cocaine-exposed neonates. This article reviews the reproductive risks associated with prenatal cocaine use. The pharmacology and physiology of cocaine in relation to pregnancy is discussed, and the impact of this substance on the growth and development of the fetus and infant is reviewed.

Key words: behaviour/cocaine/outcome/pregnancy/teratogenesis

Introduction

The stimulant properties of cocaine have been recognized for >1000 years, and the toxicity and addictive potential of this drug have led to the stricter regulation of its use. Western society is in the midst of the fifth and largest epidemic of stimulant use since 1890 (Gawin and Ellinwood, 1988). A Medline search for published medical research and epidemiological studies concerning cocaine abuse in human subjects during the past 20 years revealed a 100-fold increase in cocaine-related investigations (Figure 1). The surge in basic science and clinical research seen in the USA may be followed by a similar trend in Europe over the next decade. Therefore, we present a critical analysis of the body of knowledge concerning the interactions between cocaine and human reproduction, from conception through to infant outcome, and have attempted to strike a balance between the science and sociology of perinatal cocaine exposure.

Epidemiology

Prevalence

According to the National Institute of Drug Abuse Household Survey (National Institute on Drug Abuse, 1991), ~25% of American women aged 18–25 years report using an illicit drug. It is further estimated that nearly 30 million Americans have used cocaine at least once, and that women of childbearing age represent an increasing proportion of the 8 million people who are regular users (Clayton,

[1]To whom correspondence should be addressed. Tel: +001-334 471 7017; Fax: +001-334 471 7741

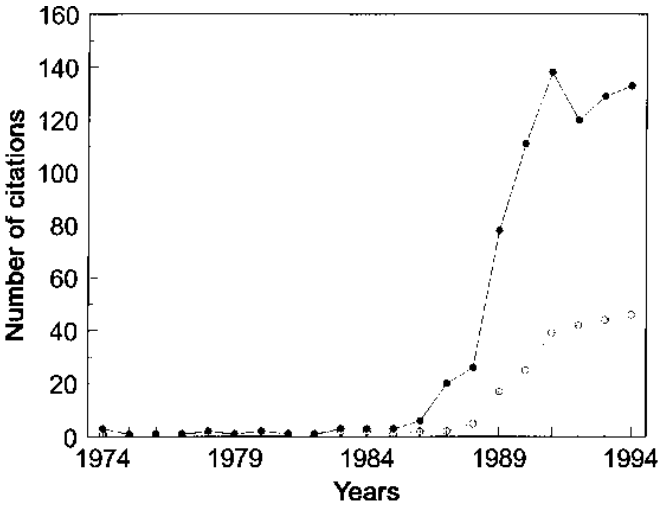

Figure 1. The number of articles written in English concerning cocaine use in pregnancy in human (—) and animal (·····) investigations published from 1974 to 1994.

1985). Cocaine use during pregnancy has increased dramatically, and in one teaching hospital a 15-fold increase in prenatal cocaine exposure occurred during a 12 year period (Streissgurth *et al.*, 1991).

Substance abuse has been reported to occur in 5–45% of pregnancies (Zuckerman *et al.*, 1989; Chasnoff *et al.*, 1990; Ostrea *et al.*, 1992; Vega *et al.*, 1993), but differences in study methodology make it difficult to estimate prevalence accurately, or demographic patterns or perinatal sequelae of cocaine use by the pregnant mother. Studies that utilize urine toxicology screening are dependent on recent exposure, and thus may not identify all users (Ostrea *et al.*, 1992). Furthermore, perinatal cocaine exposure may be underestimated in those studies which rely solely on the maternal admission of drug use (Frank *et al.*, 1988) or maternal screening based on the presence of 'risk factors' (Handler *et al.*, 1991). To complicate matters, the overall prevalence of cocaine use, as well the proportion of ethnic minorities and low socio-economic groups, may be overrepresented in studies of inner-city populations at academic centres (Zuckerman *et al.*, 1989; McCalla *et al.*, 1991). Nevertheless, the overall prevalence rate for all substances was ~5%, and the rate of cocaine use in particular was ~2%, as determined by an anonymous screening of >29 000 pregnant women at >200 community-based and teaching hospitals within the state of California (Vega *et al.*, 1993). Generally, the rate of substance abuse has been reported to be similar in patients seen at public (16%) and private (13%) prenatal clinics (Chasnoff *et al.*, 1990). In the large multicentre study conducted in the ethnically diverse state of California (Vega *et al.*, 1993), differences were found in the rate of cocaine use among various racial groups; positive screens occurred more often in black (7.8%) women than in either white (0.6%) or Hispanic (0.6%) mothers. In addition, Handler *et al.* (1991) observed that cocaine use occurred more often in multigravid women, and >60% of cocaine-positive screens occurred in pregnant mothers aged 20–29 years.

Phibbs *et al.* (1991) compared the hospital course of 355 mothers and infants who were exposed to antenatal cocaine with 199 randomly selected drug-free controls. Neonates in the cocaine-using group weighed significantly less and were significantly more likely to require neonatal intensive care than control infants. In addition, hospital costs increased 4-fold in cocaine-exposed infants, and were compounded by an increase in the time between when the infant was considered stable for discharge until actual discharge occurred. The average hospital costs for prenatally exposed infants was US $11 500 dollars, and the authors concluded that nearly US $500 million were added to USA healthcare costs as a result of maternal antepartum cocaine use.

Cocaine use during pregnancy is often associated with the use of additional legal and illegal drugs (e.g. methadone, heroin, amphetamines) which can considerably confound the interpretation of studies examining the effect of cocaine on pregnancy outcome. Marijuana, alcohol and cigarette use are increased by almost 3-fold above that found in drug-free populations of similar racial and social backgrounds (Frank *et al.*, 1988; Gillogley *et al.*, 1990; Singer *et al.*, 1991). In particular, tobacco use appears to be a significant risk factor for the use of illegal drugs, and in the study by Vega *et al.* (1993), the prevalence rate for cocaine use was >20 times higher in smokers than in non-smokers.

In addition to using multiple drugs, substance-abusing women are significantly more likely to receive inadequate prenatal care. While positive screens were identified in <1% of pregnant mothers who began care during the first trimester, cocaine use was demonstrated in 25% of women who had received no prenatal care (Vega *et al.*, 1993). Furthermore, drug use has been reported among approximately half of the women with fewer than five prenatal visits (Cherukuri *et al.*, 1988; Singer *et al.*, 1991; Broekhuizen *et al.*, 1992).

Finally, compared with drug-free populations, cocaine-using women are more likely to experience other health-related problems during pregnancy, such as syphilis (Minkoff *et al.*, 1990) and human immunodeficiency virus (Lindsay *et al.*, 1992). Furthermore, as a result of anorexia and poor maternal nutrition, anaemia is more common in women who use cocaine, and these women tend to gain less weight during pregnancy and weigh less at delivery than non-users (Matera *et al.*, 1990). These known side-effects of chronic cocaine use may also exacerbate any direct effect of cocaine on fetal growth (Frank *et al.*, 1988; Singer *et al.*, 1991).

Table I. Criteria for perinatal urine drug screening at the University of South Alabama

Physical examination	Obstetric complications	Medical complications	Social history
Altered sensorium	Preterm labour	Human immunodeficiency virus	Drug use by partner
Constricted or dilated pupils	Premature rupture of membranes	Liver disease	Incarceration
Needle track marks	Suspected fetal growth restriction	Pneumonia	Prostitution
Indurated nasal mucosa	Abruptio placentae	Pancreatitis	Domestic violence
	Intrauterine fetal demise	Sexually transmitted disease	
	Unexplained congenital anomalies	Tobacco use	
	Neonatal withdrawal symptoms		
	Erratic or no prenatal care		

Adapted from Chasnoff (1987).

Identification of exposure

Maternal questionnaire

Denial is a major component of addictive behaviour, and maternal self-report, whether prospective or retrospective, is an unreliable method for the identification of substance abuse. Frank *et al.* (1988) found that cocaine use would have remained undetected in ~25% of pregnant women if urine toxicology screening had not been performed. Christmas *et al.* (1992) reported that only 40.0% of mothers with toxicological evidence of recent cocaine use admitted to using cocaine. Even more striking was the observation by Shiono *et al.* (1995) that only 8.6% of women who were using cocaine actually tested positive for the drug.

Toxicology screening

The selection criteria for performing a perinatal toxicology screen vary greatly from hospital to hospital and from physician to physician. While the random screening of patients without clinical evidence of substance abuse may be considered unethical (American College of Obstetricians and Gynecologists, 1994), testing the mother, the neonate or both for cocaine use during pregnancy may be useful in some clinical situations, such as the presence of unexplained fetal growth restriction, unexpected prematurity or abruptio placentae, even when cocaine use had not been suspected previously. The criteria used for perinatal toxicology screening at our hospital are listed in Table I.

Urine toxicology screening

The importance of biological markers for identifying illicit drug use is now well recognized by both clinicians and researchers. The most commonly used test of either maternal or infant urine is the enzyme-mediated immunoassay technique (EMIT). The EMIT will detect benzoylecgonine, a cocaine metabolite, in the urine of non-pregnant adults for 24–72 h after use (Hamilton *et al.*, 1977), although the rapid clearance of cocaine may limit the ability of this test to identify all gravid cocaine users. A survey of urine drug test results in mothers and newborn babies demonstrated that the clinical suspicion of drug involvement may be confirmed in about two-thirds of the cases when either the mother or the newborn baby is tested (Osterloh and Lee, 1989). However, testing both the mother and newborn baby increases the identification of cocaine use to 85%, suggesting that both maternal and neonatal testing may be indicated in most cases (Osterloh and Lee, 1989).

Hair analysis

Testing maternal and/or neonatal hair for cocaine metabolites has been proposed as an alternative method for identifying previous cocaine exposure when urine samples are negative for drug metabolites at delivery (Bailey, 1989; Graham *et al.*, 1989). However, the risks of contamination of adult hair through the passive environmental exposure to illicit drugs are unknown, and the accurate identification of drugs may be altered by chemicals applied for cosmetic purposes. These limitations, together with the fact that the amount of neonatal hair required for testing may be unacceptable to parents, render the currently available methods of hair analysis to be of questionable utility for most research and clinical purposes (Bailey, 1989).

Meconium analysis

The radioimmunoassay of meconium for cocaine, marijuana and opiate metabolites has been proposed as an accurate method for the determination of perinatal drug exposure. Drug metabolites accumulate in meconium through the fetal ingestion of the drug from the amniotic fluid and direct deposition in fetal bile (Ostrea *et al.*, 1992). Although the analysis of meconium cannot pinpoint the gestational week of exposure, this testing can be used to quantify the cumulative fetal dosage from the period of meconium production, i.e. ~18–20 weeks prior to delivery. Meconium testing reportedly reduces the frequency of false-negative urine screens, particularly in mothers who have abstained from drug use for a few

days prior to delivery (Ostrea *et al.*, 1992). However, meconium testing is not universally available, and this method is associated with a number of technical difficulties, including the gestational age at which fetuses can produce benzoylecgonine, the distribution of metabolites in a meconium specimen and the preparation and number of samples required for assay. Ostrea *et al.* (1992) have reported that drug metabolites continue to be found in stools collected on the second and third day following delivery, and interpretation may be confounded by exposure through breast feeding or passive inhalation.

Pharmacology

Physical chemistry and preparation

Cocaine, a methyl ester, is an alkaloid derived from the *Erythroxylon coca* plant that is found in certain areas of Central and South America (Dattel, 1990). The alkaloid dissolves in hydrochloric acid to become a water-soluble salt, cocaine hydrochloride, and is often mixed with other substances that may alter or enhance its effects (Bingol *et al.*, 1987). In this form, it is ~90% cocaine by weight, decomposes on heating and melts at 195°C. Cocaine hydrochloride is marketed in a crystalline form or as a powder that is most often ingested by injection or inhalation (Delaney-Black *et al.*, 1994). As a result of the acidic environment of the stomach, cocaine is poorly absorbed via the oral route. The nearly water-insoluble form of cocaine, 'free base' or 'crack', is an odourless, transparent crystalline substance that melts at 98°C (Delaney-Black *et al.*, 1994). Crack is absorbed well from all sites, including mucous membranes and the gastro-intestinal tract, resulting in a rapid onset of sustained duration of euphoria (Bingol *et al.*, 1987). Because crack vaporizes at higher temperatures, it is not destroyed by heating and can readily be ingested by smoking (Dattel, 1990). Effective absorption into the pulmonary vasculature and a rapid increase in the concentration of cocaine occur when smoked, and results in physiological effects similar to those produced by i.v. cocaine. While the effects of intranasal cocaine administration last for 1–2 h, the euphoria associated with smoking cocaine lasts only ~20 min (Cregler and Mark, 1986). Crack cocaine is technically simpler and less expensive to prepare than cocaine hydrochloride, which has contributed to the widespread availability of this drug (Dattel, 1990).

Pharmacological effects

Cocaine inhibits the permeability of the cell membrane to sodium and prevents the initiation and conduction of electrical impulses within nerve cells. This pharmacological action is responsible for the widespread use of cocaine as a local anaesthetic since the late 1800s (Moore *et al.*, 1986). In contrast, the neurological effects of cocaine result from its sympathomimetic activity, in which the presynaptic re-uptake of norepinephrine and dopamine is inhibited. This mechanism produces an excess of neurotransmitter at the postsynaptic receptor sites (Roe *et al.*, 1990), and results in vasoconstriction, an acute rise in arterial blood pressure, tachycardia (Moore *et al.*, 1986) and a predisposition to ventricular arrhythmias (Cregler and Mark, 1986) and seizures (Kramer *et al.*, 1990).

The dopaminergic effects of cocaine produce both euphoria and addiction (Bandstra and Burkett, 1991), and acutely create a heightened sense of power and sexual excitement (Nunes and Rosecan, 1987). However, chronic use may cause dopamine depletion at the pre- and postsynaptic receptors (Bandstra and Burkett, 1991), resulting in the dysphoria that develops during withdrawal and the subsequent craving for more drug (Gawin and Kleber, 1984). In this way, alterations in dopamine neurotransmission may contribute to the development of compulsive-use patterns. Moreover, serotonin biosynthesis is impaired with chronic cocaine use, and may enhance the excitatory effects of dopamine and decrease the need for sleep secondary to its effect on the sleep–wake cycle (Bandstra and Burkett, 1991).

Cocaine metabolism

Elimination and detoxification of cocaine into its major metabolites occur principally by non-specific plasma and tissue esterases (Figure 2). Cocaine is partially metabolized (20%) by *N*-demethylation to norcocaine, which is a more potent inhibitor of norepinephrine re-uptake than the parent drug (Hawks *et al.*, 1974; Stewart *et al.*, 1978). Plasma and liver esterases and microsomal mono-oxygenases appear to account for the remaining metabolism of cocaine and norcocaine into the major metabolites, benzoylecgonine and ecgonine methyl ester (Stewart *et al.*, 1979). These two metabolites are more polar and are readily excreted by the kidneys and the gastro-intestinal tract (Frank *et al.*, 1993). Plasma cholinesterase activity is much lower in fetuses, infants, elderly men, patients with liver disease and pregnant women (Stewart *et al.*, 1979). Roe *et al.* (1990) have suggested that the low or absent cholinesterase activity seen in 1–13% of normal adults might account for some of the reported variability in cocaine toxicity. Furthermore, the simultaneous use of alcohol and cocaine results in the production of cocaethylene by the liver (Randall, 1992), which has a longer half-life than cocaine and has been associated with a greater risk of sudden death in adult users. Cocaine has a plasma half-life of ~90 min and produces tachyphylaxis, as shown by a rapid decline in the effect of the drug despite its continued presence in the circulation. As a result, the half-life of cocaine, in terms of the euphoria it produces, is <45 min (Seigel, 1982). Therefore, to

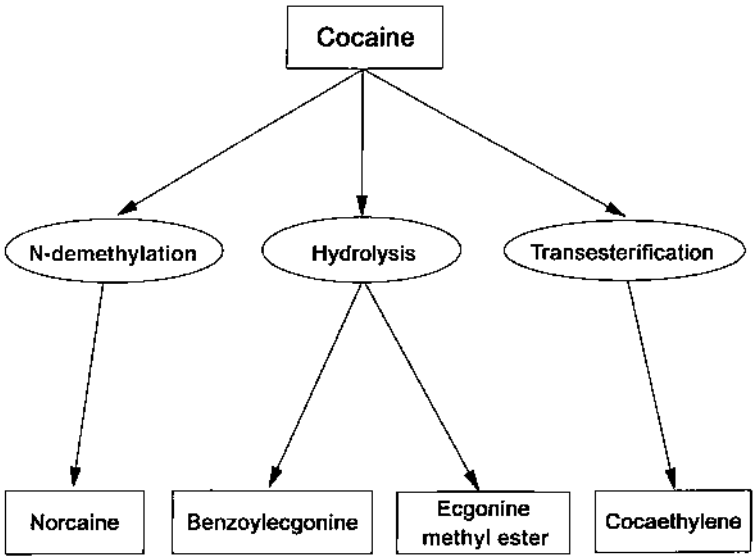

Figure 2. Schematic representation of the metabolism of cocaine into major metabolites.

maintain its euphoric action, cocaine has to be used repeatedly, even as often as every 10 min.

Several recent studies have explored the capacity of the placenta to serve as a protective barrier to the fetal effects of cocaine exposure. Schenker *et al.* (1993) described the rapid transfer of cocaine and the metabolites cocaethylene and norcocaine across the placenta through passive diffusion. While no mechanism for the placental biosynthesis of cocaine could be identified by Schenker *et al.* (1993), Roe *et al.* (1990) suggested that the concentration of cocaine *in vitro* was decreased by placental microsomes, and that this effect was not altered by enzyme inhibition, e.g. anticholinesterase. It is worth noting that fetal growth may be altered by the binding of cocaine to placental microvillous membrane vesicles, which is associated with a reduction in the concentration of sodium-dependent amino acid transporters (Dicke *et al.*, 1994).

Amniotic fluid as a reservoir for cocaine

In the last half of pregnancy, amniotic fluid volume represents a balance between intramembranous transport and fetal urination, swallowing and lung fluid production. Recent studies suggest that fetal exposure to the vasoactive effects of cocaine and/or its metabolites may be prolonged because of the presence of these substances in amniotic fluid (Jain *et al.*, 1993).

Using solid-phase extraction techniques, Jain *et al.* (1993) identified cocaine and/or benzoylecgonine in the amniotic fluid of ~75% of subjects who used cocaine during the last 2 months of pregnancy. While the concentration of cocaine was similar in amniotic fluid and neonatal urine, benzoylecgonine was found in significantly greater concentrations in amniotic fluid than in neonatal urine. Mahone *et al.* (1994) administered cocaine directly into the amniotic fluid of nine pregnant ewes, and the concentrations of cocaine, benzoylecgonine, ecgonine methyl ester and norcocaine in amniotic fluid, maternal plasma and fetal plasma were measured serially. The concentration of cocaine and metabolites in fetal plasma was significantly less than in amniotic fluid. Following the fetal oesophageal ligation of three sheep, the difference between the amount of cocaine and metabolites in amniotic fluid and plasma was unchanged. Furthermore, there was no difference between ligated and non-ligated fetuses in the concentration of cocaine, benzoylecgonine and norcocaine in meconium. As a result, Mahone *et al.* (1994) concluded that cocaine and its metabolites possibly enter the fetal circulation by absorption through the umbilical and placental surface vessels, rather than by fetal swallowing.

Teratogenesis

The developing fetus is dependent upon a functioning vascular system to provide an adequate supply of nutrients and to remove the waste products of metabolism. During organogenesis, the fetal vascular system evolves in relation to specific requirements for morphological development. As a result of the dependence on dynamic changes in vessel formation and ablation, fetal growth may be adversely affected by a number of disruptive agents (Van Allen, 1981). In particular, because fetal vessel architecture is a direct result of tissue demands and circulatory haemodynamics, exposure to the potent vasoconstrictive effects of cocaine during the first trimester may increase the risk of structural abnormalities (Stevenson *et al.*, 1987; Finnell *et al.*, 1990; Webster and Brown-Woodman, 1990).

Table II. Structural abnormalities observed in infants with in-utero cocaine exposure

Genito-urinary	Cardiac	Gastro-intestinal	Skeletal	Neurological
Ambiguous genitalia	Arrhythmias	Gastroschisis	Limb reduction	Cerebral infarcts
Cryptorchism	Atrial septal defect	Ileal atresia	Ossification delays	Choroid plexus cysts
Horseshoe kidney	Hypoplastic right heart	Imperforate anus	Skeletal defects	Hydrocephalus
Hydronephrosis	Patent ductus arterious	Jejunal atresia	Skull defects	Encephalocele
Hypospadius	Pulmonary stenosis			Exencephaly
Prune belly syndrome	Transposition of the great vessels			Microcephalus
	Ventricular septal defect			Optic dysplasia
				Porencephaly

The uterine vasculature is particularly sensitive to the vasoactive effects of epinephrine and norepinephrine (Griess and Van Wilkes, 1964; Rosenfeld and West, 1977), and this effect is enhanced by the cocaine-induced blockade of catecholamine re-uptake (Woods *et al.*, 1987). Cocaine administered to pregnant ewes caused a dose-dependent acute decrease in uterine blood flow, with a resultant decrease in fetal arterial oxygen partial pressure and oxygen content (Woods *et al.*, 1987). Furthermore, the fetal cardiovascular effects (i.e. heart rate, mean arterial pressure) may be amplified as a result of accompanying fetal hypoxaemia and the production of fetal catecholamines (Chan *et al.*, 1992). An acute reduction in uteroplacental blood flow and the direct effects of cocaine on the fetal vasculature contribute to fetal hypoxaemia and alterations in cardiovascular functioning (Gingras *et al.*, 1992). The destruction of fetal tissue and organ malformation may also occur, depending on the severity and length of the insult (Millicovsky and DeSesso, 1980). Differentiating fetal tissues, including those with a high blood flow and new or distal vessels, are the most susceptible to hypoxic injury. Uterine artery ligation in the rat model has been reported to cause fetal hypoxia resulting in haemorrhage and oedema (Webster *et al.*, 1987). Ultimately, fetal tissue loss may result from vessel rupture and haemorrhagic necrosis (Van Allen, 1981), and severe fetal haemorrhage can occur (Webster and Brown-Woodman, 1990). Therefore, at least theoretically, the vasoactive effects of prenatal cocaine exposure may be teratogenic in the developing fetus.

Cocaine as a teratogen

While a specific congenital malformation syndrome attributed to prenatal cocaine exposure has not been described, both animal and human studies have suggested an increase in the rate of a variety of congenital malformations in the offspring of pregnant mothers exposed to antenatal cocaine. Morphological alterations which have been described in the fetuses and neonates of cocaine users are summarized in Table II.

Results from animal studies suggest that fetal malformations related to maternal cocaine administration are dose dependent and are the result of haemorrhage and oedema and ultimately hypoxia. Exencephaly, cryptorchism and skeletal and orbital defects were found in the fetuses of pregnant mice that were given daily doses of cocaine from days 7 to 12 of gestation (Mahalik *et al.*, 1980). Neurological, gastro-intestinal, urogenital, renal and cardiovascular anomalies were observed in those fetal mice exposed to high doses of i.p. cocaine (Finnell *et al.*, 1990). Church *et al.* (1988) administered increasing daily doses of cocaine to mice until day 19 of gestation, and reported two fetal anomalies (anophthalmia and microcephaly), and an increase in fetal oedema and cephalic haemorrhage. Using a rat model, Webster and Brown-Woodman (1990) observed that cocaine hydrochloride administered to the pregnant dam induced severe haemorrhage and oedema in the tail and hindlimbs of fetal pups during the late organogenesis period.

Because of inherent problems associated with study control, a direct causative effect of maternal cocaine use on the development of congenital anomalies in human fetuses is much more difficult to determine. Nevertheless, recent controlled investigations have suggested a relationship between prenatal cocaine use and a diversity of fetal structural malformations. Bingol *et al.* (1987) reported a greater incidence of cardiac anomalies (transposition of the great vessels, hypoplastic right heart) and skull defects (parietal bone, exencephaly) in the fetuses of 50 cocaine users compared with >3000 fetuses of drug-free pregnant women. An increased rate of genito-urinary and gastro-intestinal tract defects (prune belly syndrome, hypospadius, ureteral displacement, ileal atresia) was noted in a group of fetuses exposed to cocaine during the first trimester compared with the rate of these malformations in fetuses whose mothers had used multiple substances other than cocaine during pregnancy (Chasnoff *et al.*, 1989c). In a comparison of the

offspring from cocaine and drug-free mothers, Lipshultz *et al.* (1991) found significant cardiac malformations (pulmonic stenosis, patent ductus artriosus, septal defects) in the cocaine group. Moreover, fetal exposure to cocaine has been observed to increase the rate of central nervous system haemorrhage, ischaemia and degeneration (Dixon and Bejar, 1989; Dogra *et al.*, 1994). However, these findings are not consistent in all studies, and in two prospective investigations there was no difference in the occurrence of fetal anomalies between study and control populations (Hadeed and Siegel, 1989; Rosenstein *et al.*, 1990).

Maternal and fetal cardiovascular effects of cocaine

The number of perinatal complications associated with cocaine use during pregnancy has led to animal studies designed to delineate the effect of cocaine on the maternal and fetal cardiovascular systems. The cardiovascular effects of cocaine are thought to be mediated primarily through cocaine's ability to block the re-uptake and degradation of norephineprine and dopamine at adrenergic nerve endings (Bayorh *et al.*, 1983). The uterine vasculature has a rich supply of sympathetic adrenergic nerve fibres which readily constrict in response to catecholamine stimulation (Plessinger and Woods, 1990). In a sheep study, Woods *et al.* (1987) administered incremental doses of i.v. cocaine to the ewe and fetus, and found that cardiovascular responses occurred in a dose-dependent manner. Maternal mean arterial pressure (MAP) peaked within 2 min following injection, and was associated with a concurrent increase in uterine vascular resistance and a decrease in uterine blood flow. Following maternal injection, the fetal oxygen partial pressure and oxygen content decreased significantly, and there was an associated increase in fetal heart rate and MAP. While fetal tachycardia and hypertension occurred following the direct fetal administration of cocaine, no significant fetal hypoxaemia was observed. In a subsequent investigation, Woods and Plessinger (1990) demonstrated the rapid transfer of cocaine across the placenta following maternal administration. The results of these studies suggest that cocaine may affect the fetal cardiovascular system indirectly by a hypoxaemic-induced release of catecholamines, and directly by the vasoconstriction of fetal blood vessels.

Subsequent studies (Plessinger and Woods, 1990; Woods and Plessinger, 1990) have suggested that pregnancy may exacerbate the cardiovascular effects of cocaine in the mother. Compared with the non-gravid sheep, significantly lower doses of i.v. cocaine were required in the pregnant ewe to produce abruptio placentae, cardiac arrhythmias, respiratory distress, seizures and death. Using non-toxic doses of cocaine in pregnant and non-pregnant ewes, Woods and Plessinger (1990) found a dose-dependent increase in blood pressure in both groups, although pregnant ewes demonstrated significantly greater sustained increases in MAP than non-pregnant animals.

To delineate further the mechanisms underlying these actions, Plessinger and Woods (1990) administered progesterone for 3 days to non-pregnant ewes. Although similar changes in blood pressure and heart rate were observed following i.v. norepinephrine administration before and after progesterone treatment, suggesting that α-adrenergic activity was not enhanced by progesterone, a significant increase in heart rate and blood pressure was observed in the progesterone-treated group when cocaine was given. Subsequently, Woods *et al.* (1994) reported that compared with non-pregnant animals, cocaine administered to pregnant ewes produced a significantly greater increase in maternal heart rate, systemic vascular resistance and cardiac oxygen consumption, as well as a significant decrease in cardiac output and stroke volume. Furthermore, serum concentrations of cocaine in the pregnant sheep were 10-fold higher at 5 min following i.v. injection than in controls.

To minimize the confounding effects of hypoxaemia, via cocaine-induced reductions in uterine blood flow on the fetal cardiovascular response, Chan *et al.* (1992) injected cocaine directly into the great vessels of fetal lambs. Plasma cocaine values peaked within 5 min following injection and had completely cleared by 1 h. There was an associated increase in fetal blood pressure and a resultant fetal bradycardia followed by a sustained tachycardia. While fetal catecholamine concentrations rose in a dose-dependent manner, the increase in epinephrine was not significant, but a 2-fold increase in fetal norepinephrine concentrations occurred at high cocaine doses. These findings support the premise that there is a direct effect of cocaine on the fetal cardiovascular response.

The results of these animal studies suggest that during pregnancy the maternal cardiovascular system is significantly more sensitive to the actions of cocaine. The considerably enhanced response to cocaine during gestation is most probably a consequence of pregnancy-associated changes in α-adrenergic activity and cocaine metabolism. Furthermore, in addition to cocaine-induced fetal hypoxaemia, cocaine crosses the placenta and may have a direct effect on fetal circulation.

Effects of parental cocaine use

Paternal drug use

Although the effects of paternal drug use have not been assessed in terms of infant outcome, it appears that cocaine

binds *in vitro* to human spermatozoa (Yazigi *et al.*, 1991). The use of cocaine for ≥5 years is associated with a decrease in sperm concentration and motility, as well as an increase in the proportion of abnormal sperm forms, even after considering other major risk factors for male subfertility (Bracken *et al.*, 1990). Sexual partners of drug-using women are more likely to be drug users than are partners of non-users (Amaro *et al.*, 1990). Because substance-abusing women often have multiple sexual partners, it may be difficult to identify a child's biological father, and thus the estimation of the effects of paternal drug use on perinatal outcome is confounded (Frank *et al.*, 1993). Furthermore, cocaine users have an increased risk for tubal factor infertility, presumably as a result of the increased rate of sexually transmitted diseases observed in regular users (Mueller *et al.*, 1990).

Maternal cocaine use and obstetric complications

The association between cocaine use and poor obstetric outcome is somewhat controversial, and this discrepancy relates to differences in study design, screening techniques, maternal socio-economic status and life style, and outcome measures. A variety of perinatal complications have been associated with cocaine exposure, including spontaneous abortion, preterm labour, preterm premature rupture of membranes, low birth weight, placental abruption and fetal growth restriction. However, as a result of the multiple factors associated with substance abuse, attributing poor perinatal outcome to a single cause is problematic.

In general, three mechanisms, directly related to an increase in sympathetic tone, may be responsible for the increased incidence of obstetric complications in association with cocaine: (i) placental vasoconstriction and the resultant decrease in fetal oxygen supply; (ii) abrupt increases in maternal blood pressure; and (iii) increased uterine activity.

Spontaneous abortion

An increased rate of spontaneous abortion has been reported in mothers using cocaine on a regular basis. Chasnoff *et al.* (1985) found that women who used cocaine alone or in combination with other substances had a spontaneous abortion rate of ~40%, which was significantly greater than that of non-users or women who used only opiates. Similar findings have been reported in more recent retrospective studies (Keith *et al.*, 1989; MacGregor *et al.*, 1989). However, Gillogley *et al.* (1990) found that when primigravid women were excluded from the analysis, there was no increase in the rate of spontaneous abortion in cocaine users compared with controls.

Preterm labour

In general, the neonatal complications of prematurity are responsible for the majority of adverse perinatal outcomes. Although the specific effect of cocaine use on uterine activity is unknown, preterm contractions may result from chronic catecholamine exposure and down-regulation of the myometrial β-adrenergic receptors (Smith *et al.*, 1995). The rate of preterm delivery associated with cocaine use has been reported to be ~30%, which is significantly increased above that in drug-free controls (Chasnoff *et al.*, 1989a; Gillogley *et al.*, 1990; McCalla *et al.*, 1991; Spence *et al.*, 1991; Miller *et al.*, 1995).

The impact of dual or poly-substance abuse has been suggested as a causative mechanism in preterm birth. In a recent prospective multicentre cohort study, Shiono *et al.* (1995) found no difference in the rate of preterm birth between women who used cocaine, tobacco and/or alcohol, and controls. Conversely, Kliegman *et al.* (1994) compared the effect of demographic variables (e.g. race, payment source) and substance abuse (e.g. cocaine, marijuana, tobacco) on preterm birth using multivariate logistic modelling; they found that only cocaine use was a significant predictor of prematurity.

Preterm premature rupture of membranes (PPROM)

Keith *et al.* (1989) found that the incidence of PPROM was higher in women who used cocaine alone or cocaine and opiates than in drug-free controls. Similar results were reported by Miller *et al.* (1995), who found that >20% of mothers who used cocaine developed PPROM compared with 3% of drug-free mothers. Dinsmoor *et al.* (1994) found that 23% of patients admitted with PPROM were positive for cocaine alone or cocaine plus some other substance, and that PPROM associated with recent cocaine use was associated with greater cervical dilatation at admission and a shorter latency period to labour. In contrast, Oro and Dixon (1987) compared cocaine users with control patients from a general obstetric clinic, matched for prenatal care status, and found no increase in the risk of PPROM.

Placental abruption

Decreases in uterine and placental perfusion associated with cocaine can clearly have an adverse effect on the placental–fetal unit. Multiple clinical studies designed to evaluate the relationship between cocaine and placental abruption have appeared in the literature. In one of the larger studies, Bingol *et al.* (1987) compared two user groups (50 persons using cocaine only, 110 using cocaine plus other drugs) with 340 drug-free controls. They found that placental abruption occurred significantly more often in association with cocaine only use or cocaine and other

drugs. Similarly, Chasnoff *et al.* (1985) reported that the incidence of abruption was significantly higher among women who used cocaine (17%) compared with the incidence among drug-free mothers (0%). Interestingly, while women who used cocaine throughout pregnancy were more likely to experience placental abruption than those who stopped using cocaine after the first trimester, the use of cocaine during the first 12 weeks of gestation only was still associated with an increased rate of placental abruption. Furthermore, when subjects who used tobacco were excluded from consideration, cocaine use was strongly associated with abruptio placentae in a recent multicentre study (Shiono *et al.*, 1995). Histological studies of the placentae of cocaine users have failed to disclose any specific morphological alterations.

Fetal growth restriction

The most consistent finding regarding in-utero cocaine exposure is that of impaired somatic growth and decreased head circumference (Delaney-Black *et al.*, 1994). In the majority of reports, gestational age, birth weight, head circumference, and length were decreased and the incidence of low birth weight was increased in the offspring of cocaine-using women (Chouteau *et al.*, 1988; Hadeed and Siegel, 1989; Gillogley *et al.*, 1990; Petitti and Coleman, 1990; McCalla *et al.*, 1991; Spence *et al.*, 1991; Racine *et al.*, 1993). Studies have found depressed neonatal fat stores and a lower lean body mass in cocaine-exposed infants after controlling for maternal weight/height and pregnancy weight gain (Frank *et al.*, 1993). Maternal cocaine use was also associated independently with a reduced head circumference in a large prospective survey in Boston, MA, USA (Zuckerman *et al.*, 1989). This finding was of particular concern because all mothers received prenatal care. Fetal growth restriction associated with maternal cocaine use has been ascribed to its generalized vasoconstrictive effects and the reduction of nutrient transfer and availability across the maternal fetal-facing plasma membranes of the syncytiotrophoblast (Dicke *et al.*, 1993). The ability of cocaine to interfere with sodium-dependent amino acid transport in these membranes may represent an additional mechanism through which cocaine deprives the fetus of essential substrates for growth.

Pre-eclampsia/eclampsia

Monga *et al.* (1994) demonstrated that the addition of cocaine to placental tissue from healthy women altered the thromboxane:prostacyclin ratio in a dose-dependent manner, similar to that seen in pre-eclampsia patients. The effects of increased thromboxane production result in placental vasoconstriction and reduced uteroplacental blood flow, and may enhance the vasoactive sequelae of cocaine. The clinical correlation of these findings is supported by Towers *et al.* (1993), who reported their results for 11 women with positive urine cocaine screens and physical findings consistent with pre-eclampsia and/or eclampsia (e.g. hypertension, headache, visual changes, seizures). While each of these patients was started on i.v. magnesium sulphate, the symptoms quickly abated and treatment was discontinued. These findings suggest that physiological manifestations of cocaine use during pregnancy may simulate those associated with pre-eclampsia.

Cocaine bingeing and pregnancy outcome

Burkett *et al.* (1994) studied cocaine and crack bingeing (use from 20–34 h) patterns in 905 pregnant women to determine the effect of the pattern of cocaine use on perinatal outcome. Patients were categorized according to bingeing patterns: group I consisted of 78 women with 'erratic' bingeing, i.e. variable in intervals, duration and amounts; group II included 67 women who binged daily; and group III consisted of 760 women who binged in cycles at 3 day, 3–7 days, weekly or greater intervals. Although complications were highly significant in relation to the frequency of bingeing, there was no difference in the prematurity rate in groups I and II. Erratic users most often exhibited acute problems (e.g. vaginal bleeding, abruptio placentae, stillbirth), while chronic problems were more frequently associated with regular users (e.g. small for gestational age infants, maternal anaemia and maternal weight <45 kg).

Neonatal and infant effects of maternal cocaine use

Cardiovascular effects

Maternal cocaine consumption has been associated with a variety of fetal and neonatal cardiovascular sequelae, including structural anomalies (Bingol *et al.*, 1987; Lipshultz *et al.*, 1991), haemodynamic changes (van de Bor *et al.*, 1990) and persistent hypertension (Horn, 1992). In addition, fetal and neonatal arrhythmias (e.g. supraventricular tachycardia) were described in 13 cocaine-exposed infants, in association with newborn congestive heart failure (38%) and cardiopulmonary arrest (15%) (Frassica *et al.*, 1994).

Respiratory abnormalities

Abnormalities in respiratory pattern occur more frequently in cocaine-exposed infants than methadone-exposed infants (Chasnoff *et al.*, 1989b), and neonates with antepartum cocaine exposure have a greater frequency of abnormal hypoxic arousal and hypercarbic ventilatory responses than normal control infants (Gingras *et al.*, 1994).

These respiratory changes have been suggested as a predisposing factor in the pathogenesis of sudden infant death syndrome (SIDS), which has been reported to occur in 15% of infants exposed prenatally to cocaine (Chasnoff *et al.*, 1987). However, combined data from subsequent studies, using larger, more representative samples that were not controlled for tobacco use, indicate that the risk of SIDS was only 8.5 per 1000 infants (Bauchner *et al.*, 1988; Ward *et al.*, 1990). Although this risk is still elevated, it does not approach the level of risk for SIDS found among heroin- or methadone-exposed infants (15–20 per 1000) and is only slightly higher than that reported for children living in poverty (Bauchner *et al.*, 1988).

Gastro-intestinal and renal effects

Gastro-intestinal and renal abnormalities have been attributed to the vasoconstrictive effects of fetal cocaine exposure. Vascular disruption has been associated with an increased incidence of necrotizing entercolitis in human (Downing *et al.*, 1991) and rat newborns (Buyukunal *et al.*, 1994), and ileal atresia has been reported to occur more frequently in cocaine-exposed infants than in non-exposed neonates (Hoyme *et al.*, 1990). Moreover, fetuses exposed to prenatal cocaine demonstrated significantly higher renal artery resistance and decreased hourly urine production than normal controls (Mitra *et al.*, 1994).

Central nervous system effects

Fetal brain growth has been reported to be reduced following maternal prenatal cocaine use (Zuckerman *et al.*, 1989; McCalla *et al.*, 1991), and these fetuses have a greater risk for asymmetric growth restriction because the head circumference is often significantly reduced in comparison with birth weight. According to Kosofsky *et al.* (1994), brain growth is the best indicator of the extent of fetal cocaine exposure.

Fetal cerebral vessels may be particularly vulnerable to the increase in blood flow associated with the vasoactive effects of cocaine (van de Bor *et al.*, 1990). Ultrasound studies of the newborn brain have suggested an increased frequency of haemorrhagic and ischaemic lesions (e.g. intraventricular haemorrhage, cerebral infarction) in infants exposed to prenatal cocaine (Dixon and Bejar, 1989). Furthermore, infants with evidence of antenatal cocaine exposure were more likely to demonstrate cortical infarctions than controls (Heier *et al.*, 1991).

Neurobehavioural effects

In-utero cocaine exposure has been described as a behavioural teratogen, but because of confounding factors (i.e. nutrition, multiple drug use, maternal–infant interaction) the long-term effects of cocaine on infant and child neurobehavioural development remain unclear. The occurrence of a neonatal cocaine withdrawal syndrome has been suggested (Bingol *et al.*, 1987; Fulroth *et al.*, 1989), and has been described as increased irritability, high-pitched crying and vigorous sucking. Oro and Dixon (1987) reported that infants exposed to stimulants, cocaine and/or amphetamines, exhibited disturbed sleep patterns, feeding difficulties and hypertonia, and scored higher than control infants on an abstinence scale. However, subsequent studies (Dixon and Bejar, 1989; Hadeed and Siegel, 1989) have been unable to confirm these results, suggesting that behavioural differences in cocaine-exposed neonates may actually result from a residual drug effect.

At 3 days of postnatal age, cocaine-exposed infants were more likely than control infants to demonstrate increased irritability, jitteriness and tremors (Doberczak *et al.*, 1988; Chasnoff *et al.*, 1989a), and cocaine-exposed neonates exhibited poor motor control, orientation and state regulation at 12–72 h of age (Chasnoff *et al.*, 1989c). Infants exposed to cocaine have also been reported to have a significantly greater risk for motor dysfunction (Neuspiel *et al.*, 1991) and to have significant differences in muscle tone, reflex and volitional movements (Schnider and Chasnoff, 1992). However, Richardson and Day (1991) could find no difference in scores on the Brazelton (1984) Neonatal Behavioral Assessment Scale of cocaine-exposed and control infants, and no difference in neonatal jitteriness has been reported in drug-exposed and control infants (Parker *et al.*, 1990).

Chasnoff (1989) reported significant differences in orientation and state regulation between cocaine-exposed and drug-free infants at 1 month of age. While there was no difference in motor control demonstrated by cocaine-exposed infants and by controls at 3, 7 (Rangel-Friedman, 1990) and 12 months of age (Hurt *et al.*, 1995), infants exposed to prenatal cocaine demonstrated less language comprehension than controls at 1 year of age (Lapke *et al.*, 1992). In contrast, cocaine-exposed infants failed to demonstrate significant differences in the Bayley (1969) Scales of Infant Development when compared with control infants at 24 and 30 months of age (Chasnoff *et al.*, 1992; Hurt *et al.*, 1995). Furthermore, head circumference has been reported to be significantly smaller in cocaine-exposed children than drug-free infants between 6 and 30 months of age (Chasnoff *et al.*, 1992; Hurt *et al.*, 1995).

Conclusion

The dramatic increase in perinatal cocaine abuse in the USA represents a significant healthcare problem, particu-

larly for the pregnant mother and her offspring. Pregnant women who use cocaine are less likely to seek prenatal care and more likely to experience spontaneous abortion or produce low birth weight and/or premature infants. While the abuse of multiple substances, including alcohol and tobacco, confounds the interpretation of results from human investigations, the direct effect of cocaine on the mother and fetus is well described in animal models. Infants and children who are exposed *in utero* to cocaine exhibit a greater frequency of structural anomalies and demonstrate significant decreases in growth compared with drug-free populations. However, the long-term developmental effects of antenatal cocaine exposure remain poorly defined.

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