Cocaine Abuse in the Parturient and Effects on the Fetus and Neonate

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In the last decade, cocaine abuse has reached epidemic proportions. Approximately 30 million people or 15% of the US population have tried cocaine at least once, and 5 million are regular users (1). The prevalence of cocaine abuse in the obstetric population ranges from 7.5% to 45% (2–11). The widespread use of cocaine has resulted in an increase in both maternal and neonatal morbidity and mortality (2,3,5–7).

Because pregnant patients who use cocaine may require anesthesia more frequently than those who do not (12), a thorough understanding of the consequences of cocaine abuse is essential. This review will describe the pharmacology of cocaine abuse in pregnancy, the different effects of cocaine on the parturient, fetus, and neonate, and the anesthetic considerations in these patients.

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Pharmacology

The Pharmacology of Abuse

Cocaine is an alkaloid derived from the leaves of the South American shrub *Erythroxylon coca*, and is prepared by dissolving the alkaloid base to form a water-soluble salt (cocaine hydrochloride) that can be marketed as crystals, granules, or white powder (13).

There are four main routes of cocaine administration. The oral route is the oldest and is well documented by historical data, such as reports on the chewing of coca leaves by South American natives (14). After oral ingestion, the bioavailability of cocaine is 30%–40%, with an onset of 10–20 min for euphoric effects. A more common method of taking cocaine is via the intranasal route, so-called "snorting" or "sniffing." Peak plasma levels are obtained in less than 15 min, although the onset of clinical effects may be more rapid (15). Intravenous administration of cocaine hydrochloride provides a peak effect within 3–5 min (16). The most popular form of cocaine is prepared by heating cocaine hydrochloride with baking soda and water to yield free base cocaine ("crack"). This alkaline form can be 95% pure, and when smoked, provides an intense euphoria in less than 1 min with a duration of only 5–10 min (17).

Mechanisms of Action As a local anesthetic, cocaine prevents the rapid increase in cell membrane permeability to sodium ions during depolarization and blocks the propagation of action potential (18). Like other local anesthetics, cocaine may produce a negative inotropic and chronotropic effect on the heart muscle. Cocaine can impair the reuptake in the brain of dopamine and serotonin as well as tryptophan (13). The accumulation of dopamine in the synaptic cleft and stimulation of dopamine neurotransmission may lead to acute euphoria and increased alertness (13). Cocaine may also interfere with presynaptic catecholamine uptake and result in activation of the sympathetic system, e.g., tachycardia, hypertension, vasoconstriction, diaphoresis, mydriasis, hyperthermia, hyperglycemia, and tremor.

The metabolism of cocaine occurs primary through plasma and hepatic cholinesterase; less than 5% is excreted unchanged in the urine (13). Ecgonine methyl ester and benzoylecgonine constitute over 80% of cocaine metabolites and are detected in the urine for 14–60 h after cocaine use. Demethylation of cocaine in the liver yields norcocaine, an active metabolite with significant agonist activity (13). Elimination half-life values ranges from 16 min to 2 h using animal and human models and different routes of administration (19–21). Although the half-life appears to be dose-dependent (19), this alone cannot account for the great variability in the studies. Perhaps this is a reflection of variable cholinesterase activity in the animals studied. In humans, elimination half-life is 40–80 min. Inaba reported that the elimination half-life of cocaine ranged from 30 to 66 min after intravenous administration and 54–90 min after the nasal or oral route (22).

The Pharmacology in Pregnancy

Cocaine pharmacokinetics may be distinct in parturients (19). Although there are limited human data available on the pharmacology of cocaine during pregnancy, cocaine hydrochloride has been studied extensively in gravid animals.

In pregnant guinea pigs, the elimination half-life after intravenous administration was dose-dependent and ranged from 20 min to 67 min. This is similar to the response reported in human, nonpregnant volunteers (19). Plasma half-life, however, in both the pregnant ewe and fetus ranges from 4 min to 5.6 min, in contrast to the prolonged presence of its major metabolites (13,20). The volume of distribution in pregnant guinea pigs was dose-dependent and larger than that reported for nonpregnant humans (19). This larger volume of distribution in the guinea pig may be a reflection of pregnancy-related changes. Cocaine exposure may also be complicated by the reported decrease in serum cholinesterase activity during pregnancy; hence, the sustained high blood levels of cocaine in parturients (23).

Administration of cocaine to pregnant ewes results in the rapid appearance of cocaine in the plasma and fetal circulation (20,24). Cocaine has a low molecular weight, is highly lipophilic, and is poorly ionized at physiologic pH. Therefore it diffuses easily across the placenta to the fetus (25). Fetal cocaine levels reach a peak in 4–5 min after maternal intravenous administration and can be detected in the serum for 30–60 min (20,24). Fetal concentrations of cocaine reach maternal levels within 4 min (Figure 1) (20). Chronic administration of cocaine to the guinea pig model results in a similar pattern of maternal and fetal plasma cocaine concentrations (26).

Other experiments in mice and rats have reported a maternal:fetal plasma cocaine ratio as high as 3:1 after

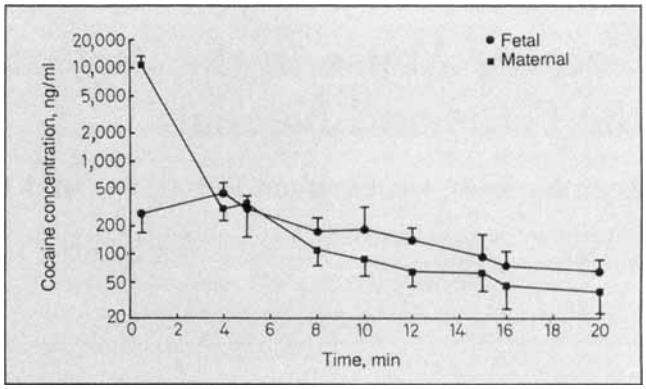

Figure 1. Cocaine plasma concentration in maternal and fetal plasma, following intravenous dose to pregnant ewes (reprinted with permission; Dev Pharmacol Ther 1991;16:123–9).

exposure (27,28). The lower fetal levels may be due to cocaine-induced placental vasoconstriction and subsequent decrease in placental blood flow or placental metabolism of cocaine (27,28). Significant cocaine accumulation occurs in amniotic fluid after chronic cocaine administration in the guinea pig (26). This may be a result of ion trapping, because amniotic fluid is generally more acidic than fetal blood (26). In experimental animals, the concentration of cocaine in various organs can be several-fold higher than that in blood (21). The brain:blood ratio of cocaine was found to range from 2:1 to 4:1 in both the fetus and the mother. Concentrations of cocaine in the fetal brain may be as high as 50%–90% of the gravid rat brain (21). These data may explain the high rate of central nervous system abnormalities among human infants.

At term, the human placenta is capable of metabolizing cocaine, presumably by the cholinesterase activity (29). This suggests that the placenta may act as a buffer and provide some degree of protection from cocaine-induced morbidity (29). The placenta also has high-affinity binding sites to cocaine, although the significance of these is not known (30). Detailed gross and histologic examination of placentas from pregnancies complicated by maternal cocaine use reveals no unique pathologic change (31).

Cocaine metabolism may be different in mother and fetus. Benzoylecgonine is the major metabolite in the guinea pig mother, whereas benzoylnorecgonine is the major metabolite in the fetus (26). Pregnant females metabolize cocaine to norcocaine to a greater extent than nonpregnant females (13). However, preliminary data in rats suggest that norcocaine, because of its high polarity, minimally crosses the placenta and has no significant effect on the fetus (32). The fetal liver can metabolize cocaine to the biologically active norcocaine, but not to ecgonine methyl ester (32). This phenomenon may be related to an immature liver and, coupled with low levels of fetal plasma

cholinesterase activity, may contribute to increased cocaine toxicity in the fetus (32).

Breast feeding provides a potential route of cocaine delivery to sucking infants (21). After intravenous administration in lactating rats, a milk:blood ratio concentration ratio of 8:1 has been observed (21). Cocaine levels in breast milk were higher than in the maternal liver or brain.

Maternal Implications

Cardiovascular Effects

Investigators have studied the effect of intravenously administered cocaine on pregnant ewes in an attempt to quantify the cardiovascular changes of cocaine use during pregnancy (24,33). Woods et al. observed dose-dependent increases in maternal blood pressure, uterine vascular resistance, and a concomitant decrease in uterine blood flow (33). These changes were observed with doses that produce plasma cocaine levels and norepinephrine concentrations typically seen in humans abusing cocaine (24). Pretreatment of gravid ewes with phentolamine did not change either the maternal blood pressure or the uterine vascular response to cocaine infusion. The investigators suggested that the vasoconstrictive effect of cocaine may be due, at least in part, to nonadrenergic mechanisms (24). Similar hemodynamic changes have been observed after intravenous administration of cocaine to gravid baboons (34).

Woods and Plessinger compared the cardiovascular response to cocaine administration in pregnant and nonpregnant ewes (35). Although both groups exhibited an increase in blood pressure and heart rate, the pregnant ewes had a twofold increase compared to the nonpregnant groups. The investigators concluded that the cardiovascular system in pregnancy exhibits increased sensitivity to cocaine, which is mediated via progesterone (36). They proposed that an increase in peripheral adrenergic sensitivity, delayed cocaine metabolism, and increased demethylation to norcocaine account for progesterone's enhancement of cocaine toxicity (36). A preliminary study in isolated papillary muscles of rats suggests that cocaine may enhance cardiac depression during pregnancy (37).

Cocaine is associated with maternal cardiovascular complications such as hypertension, myocardial ischemia, sudden maternal death, arrhythmias, and cardiac arrest (38–41). Although cocaine administration results in immediate transient elevation in maternal blood pressure, an association between cocaine abuse and pregnancy-induced chronic hypertension has not been clearly demonstrated (42–44). An increased incidence of pregnancy-induced hypertension was reported in a group of 53 cocaine-exposed pregnant women when compared with drug-free controls delivered at the same hospital (42). However, other investigators found no difference in the incidence of chronic hypertension among pregnant cocaine users (43,44).

Because treatment strategies are different, it is important to distinguish between cocaine-induced hypertension and the hypertension associated with eclampsia or preeclampsia. Cocaine-induced hypertension is characterized by lack of peripheral edema, and it may present at any time during pregnancy. In addition, severe cocaine-induced hypertension can cause the kidneys to excrete excessive quantities of protein and is associated with edema, headache, and blurred vision (40). Because obstetric patients may not admit cocaine use, the anesthesiologist should have a high index of suspicion in cases of new onset hypertension. Recently, Vertommen et al. attempted to improve uterine blood flow by using hydralazine during cocaine-induced hypertension in a pregnant ewe model (45). Although hydralazine did lower the maternal arterial blood pressure, the investigators observed a marked increase in heart rate and no change in uterine blood flow.

Intravenous cocaine users also present with cardiac valvular abnormalities during pregnancy. Henderson et al. performed echocardiograms on 23 pregnant drug users who had systolic murmurs that clinically appeared physiologic. All but two of the women demonstrated unexpected valvular changes. Although mitral valve prolapse or thickened valvular leaflets were noted in most patients, valvular vegetation on the aortic and tricuspid valves, as well as mitral regurgitation, were also described (46).

Cardiac events attributed to cocaine use in the general population include myocardial infarction, dysrhythmias, myocarditis, and aortic rupture (47,48). More than 60 cases of myocardial ischemia and infarction have been attributed to cocaine use (47,48). Most individuals who present with ischemia secondary to cocaine abuse are young, and some of them are females at child-bearing age. Dysrhythmias associated with cocaine use include sinus tachycardia, ventricular premature contractions, ventricular tachycardia/fibrillation, and asystole. Cocaine has also been reported to produce dose-related cardiac dysrhythmias in pregnant ewes at doses much lower than those in nonpregnant ewes (49). Dilated cardiomyopathy, myocarditis, and congestive heart failure have also been reported secondary to cocaine use (47,48).

Neurologic Effects

The sudden increase in arterial blood pressure after cocaine use may be the primary etiology of cerebrovascular accidents (50–52). The presumed mechanism of hemorrhage is via rupture of a preexisting aneurysm or a spontaneous bleed precipitated by the sudden surge of arterial pressure in a previously healthy person (51).

Alternatively, severe cerebrovascular spasm can produce local ischemia and necrosis, with secondary hemorrhage (50,51). Subarachnoid hemorrhage, intracerebral bleed, seizures, and rupture of aneurysm have been reported with cocaine use in pregnancy (50,53–56). Hypertension associated with seizure activity during labor may suggest recent cocaine use and not eclampsia.

Hematologic Effects

Thrombocytopenia after cocaine exposure has been demonstrated in pregnant term ewes and is related to increased levels of catecholamines associated with cocaine (57). Cocaine use in humans has also been suggested to cause severe thrombocytopenia among adult cocaine abusers (58). This may be severe enough to cause prolonged bleeding, and is unrelated to the route of cocaine administration. Cocaine-induced thrombocytopenia may be due to suppression of the bone marrow or induction of platelet-specific antibodies (58,59). Abramowicz et al. reported a case of cocaine-induced severe transient thrombocytopenia associated with hypertensive crisis in a pregnant woman (41).

Infectious Disease Considerations

A higher prevalence of syphilis and human immunodeficiency virus (HIV) infection has been found among cocaine-using parturients when compared to parturients not using cocaine (60,61). The association of these diseases with drug use is partially explained by needle sharing, which is common among addicts. However, the association between cocaine abuse and HIV is supported even after controlling for intravenous drug abuse (62). The phenomenon may be explained in part by increased sexual activity, as well as by a decrease in immunologic activity seen in cocaine abusers (62).

Endocrinologic Effects

Maternal use of cocaine may lead to metabolic and endocrine changes in both the fetus and the mother (63,64). Changes in the pregnant ewe include increases in maternal and fetal plasma glucose and lactate without alternation in plasma insulin (64). Most of the changes have been attributed to cocaine-induced release of catecholamines, as well as to fetal hypoxemia and possibly to the direct effect of cocaine. Intravenous administration of cocaine to ewes late in pregnancy is also associated with an increase in maternal plasma corticotropin (ACTH) and cortisol (63). The increase in maternal ACTH may be secondary to a direct effect of cocaine on the maternal anterior pituitary gland, or mediated via the ACTH releasing factor (63).

Table 1. Obstetric Complications Associated with Cocaine Use

- Preterm labor
- Premature rupture of membranes
- Abruptio placentae
- Spontaneous abortion
- Pregnancy-induced hypertension
- Precipitate delivery
- Stillbirth
- Meconium-stained amniotic fluid

Pulmonary Effects

Pulmonary complications occur primarily in patients who smoke free base cocaine. These include pneumomediastinum, cocaine-induced asthma, hypersensitivity pneumonitis, chronic cough, pulmonary edema, and diffusing capacity abnormalities (65,66). The most common pulmonary symptoms are cough and dyspnea, which are more prevalent in patients with impaired diffusing capacity. There does not appear to be a specific type of lung damage associated with cocaine abuse of pregnancy.

Gastrointestinal Effects

In animal models, marked elevation in serum transaminase has been observed after acute and chronic cocaine administration (67). In humans, reports are conflicting: some investigators have found histologic hepatotoxic changes, whereas others only minimal elevation of liver enzymes (67,68).

Obstetric Complications

An increased incidence of spontaneous abortion has been reported among women who abuse cocaine during pregnancy (Table 1) (69,70). Burkett et al. reviewed the obstetric outcome of 139 women who volunteered information on cocaine use during pregnancy (70). Less than 50% of the infants were live born, with spontaneous or therapeutic abortions in 41% and stillbirth accounting for 3.6%. The high spontaneous abortion rate may be related to cocaine-induced vasoconstriction, enhanced uterine contractions, and abrupt changes in blood pressure (Figure 2) (70).

Preterm labor rates are significantly higher among pregnant cocaine users (69–73). Acute cocaine use during the third trimester may result in immediate contractions, increased fetal activity, abruptio placentae, and premature labor (73). Ney et al. examined a group of patients who presented in preterm labor and compared them to a group having uncomplicated term labor (74). Urine cocaine metabolites were found in more than 17% of patients in preterm labor and less than 3%

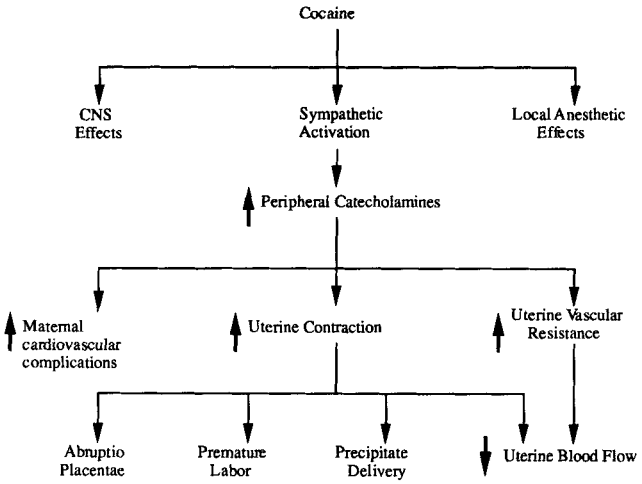

Figure 2. Cocaine exposure: Maternal effects.

of patients in the control group. Increased uterine activity and preterm labor may be related to elevated systemic catecholamine levels or to a direct effect of cocaine on the uterus (73). Cocaine has been shown to augment the α-adrenergic contractile response of the pregnant rabbit uterus *in vitro* (75).

Several studies have documented an increased rate of abruptio placentae associated with cocaine use during pregnancy (69–74). This finding may be attributed to maternal hypertension characteristic of the acute phase of cocaine abuse. The vasoconstrictive effect of cocaine may also cause a disruption in placental adherence to the uterine wall. Abruptio placentae occurs at a higher rate in cocaine-exposed pregnancies, even when the exposure is limited to the first trimester (76). Maternal hemodynamic and vasoconstrictive changes secondary to cocaine use have also been associated with rupture of ectopic pregnancy and rupture of an unscarred uterus in a laboring woman (77,78).

Cocaine can affect the condition of the fetus as well as the course of labor and delivery. An increased incidence of meconium staining, a 1.5-fold higher prevalence of prolonged membrane rupture, and an elevated risk of precipitous delivery (abnormally rapid cervical dilation) have been reported (70,71,79). Oro et al. suggested an increased incidence of neonatal distress on delivery of cocaine-exposed infants (80). The average Apgar score given at 1 min was lower among the cocaine-exposed infants, although 5-min scores were similar to those in noncocaine-exposed infants (80).

Anesthetic Considerations

Preoperative Evaluation Identifying the cocaine user during the preoperative assessment presents a special challenge to the anesthesiologist. At best, cocaine metabolites are detected in the urine for only 14–60 h after use (13). Therefore, many of the exposed mothers and infants will not be identified in a spot urine test. The technique of detecting cocaine residue in hair is more reliable, but it is expensive and difficult to perform (81). Self-reporting of drug abuse by the mother is notoriously unreliable. In recent studies among pregnant patients who used cocaine, 35%–55% denied cocaine use but had at least one positive urine assay (9,11). A history of premature rupture of membranes, smoking, alcohol use, positive syphilis serology, and use of other illicit drugs should alert the anesthesiologist to the possibility of cocaine abuse (see Table 2) (3,5,9,82).

Table 2. Maternal Characteristics Associated with Cocaine Abuse

- Multiparous
- Lack of prenatal care
- Use of other illicit drugs
- Ethanol abuse
- Cigarette use
- Positive syphilis serology

However, the single most important predictor of cocaine abuse is the absence of prenatal care (82,83). Individuals who present in labor with no prenatal care are 4 times more likely to have a positive cocaine urine test (83). Because multiple drug use is common among cocaine abusers, anesthesiologists should be aware of the various street names and mixtures of cocaine. Although the nasal absorption of drugs produces few physical findings, chronic sinusitis and ulceration of the nasal mucosa may suggest cocaine use. Sclerosis of peripheral veins and needle marks from intravenous injection may be seen. Recent cocaine injection sites have a characteristic look of multiple ecchymoses (84). Patients who are suspected of abuse need a thorough evaluation, including an electrocardiogram and possibly echocardiography for evidence of valvular disease. In cases of severe cardiovascular cocaine toxicity, general stabilization and hemodynamic control should precede induction of anesthesia (13).

Regional Anesthesia Several cases of cocaine-induced thrombocytopenia have been reported in the literature (41,58,59). Until the incidence of cocaine-induced thrombocytopenia is defined by prospective studies, a platelet count should be obtained before instituting a regional anesthetic in a cocaine-abusing parturient.

A preliminary study reported that pregnant cocaine users who received epidural anesthesia had more frequent episodes of hypotension and required more supplemental intravenous narcotics than a control group (85). Epidural anesthesia should be instituted by gradually raising the segmental level, with particular attention to hydration and uterine displacement to prevent hypotension. The hypotension secondary to regional anesthesia may be adequately treated with ephedrine. Although the chronic cocaine abuser may be catecholamine depleted and, therefore, theoretically,

unresponsive to indirect acting sympathomimetic drugs (i.e., ephedrine), this has not been proven.

The close association between cocaine use and HIV infection is an important factor when considering a regional anesthetic technique. In a recent study of pregnant HIV-positive patients who received regional anesthesia (cocaine use not specified), no adverse neurologic outcome or infections were observed (86). The authors concluded that regional anesthesia is an appropriate choice for the HIV-positive parturient.

Ester local anesthetics, which undergo metabolism by plasma cholinesterase, may compete with cocaine, resulting in decreased metabolism of both drugs (13). Cocaine users with a low dibucaine number can have slower cocaine metabolism and may be even more susceptible to cocaine toxicity (87). Cocaine also lowers the seizure threshold and may enhance the convulsant effect of other local anesthetics (88).

General Anesthesia Rapid sequence induction and laryngoscopy, commonly used in parturients, may be associated with hypertension and tachycardia more frequently among recent cocaine users. This phenomenon may be related to increased anesthetic requirements after acute cocaine exposure, as demonstrated by a dose-dependent increase of halothane minimum alveolar concentration in the dog (89). Elevated catecholamine levels secondary to both inadequate anesthesia and the presence of cocaine in the blood may result in cardiac dysrhythmias during halothane administration (13). Ketamine should be used with caution in these patients because it can markedly potentiate the cardiovascular toxicity of cocaine (13). Finally, the temperature rise and sympathomimetic effects associated with cocaine can also mimic malignant hyperthermia.

Fetal and Neonatal Implications

The administration of intravenous cocaine to pregnant ewes produces a dose-dependent increase in fetal heart rate and arterial blood pressure and a reduction in fetal Pao_2 and O_2 content (33). Direct administration into the fetal jugular vein, however, produces less of a decrease in the fetal Pao_2 or O_2 content (33). Given the larger reduction in fetal Pao_2 and O_2 content after maternal administration, the most likely etiology of fetal hypoxemia is cocaine-induced uterine vasoconstriction, which may reduce oxygen delivery to the fetus. The resultant hypoxia can stimulate the release of fetal catecholamines and increase oxygen demands. Fetal norepinephrine levels after cocaine exposure are increased both in pregnant ewes and cocaine-exposed human neonates (24,90). This cocaine-induced uterine vasoconstriction and fetal hypoxemia do not appear to be solely mediated by α-adrenergic stimulation because phentolamine does not completely eliminate the response (24).

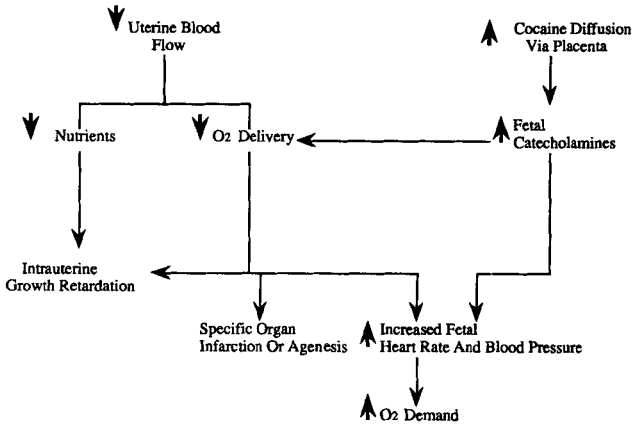

Figure 3. *In utero* cocaine exposure: Fetal effects.

Uteroplacental insufficiency results in reduced birth weight, intrauterine growth retardation, microcephaly, and prematurity (69–73,91). Several studies report an increased rate of premature delivery in women who use cocaine compared to controls (43,44,72,92). Cherukuri et al. reported that 51% of a cocaine-using parturient group delivered prematurely (93). In studies that controlled for smoking, prenatal care, and sociodemographic factors, the risk of premature delivery in exposed infants was 2.8–20 times greater than in unexposed infants (69,76,80,94). Intrauterine growth retardation and low birth weight may be related to both the length and timing of *in utero* cocaine exposure. A study conducted in infants exposed prenatally to cocaine found that exposure throughout pregnancy results in lower birth weight infants, whereas exposure limited to the first trimester has no effect (76). Decreased intrauterine growth may be the result of intermittent reduction in placental blood flow associated with maternal cocaine use (Figure 3) (76).

Target Organ Involvement

Cocaine administered to mice during organogenesis can produce fetal malformations, including skeletal defects, anencephaly, eye malformations, hydronephrosis, cryptorchidism, and delayed ossification of the skull (95). Recent animal studies demonstrate a wide variety of congenital anomalies, including dilated or immaturely developed cerebral ventricles, hydronephrosis, dilated or cystic ureters, and grossly distended bladders (96–98). There is a significant dose-related relationship between dilated cerebral ventricles, genitourinary defects, and cocaine exposure. Exposure abnormalities of the limbs, including flexion deformities and reduction of digits, have been noted as well (96–98). Gastrointestinal defects include ileal atresia as well as abnormalities of the pylorus and colon. Cardiovascular defects are frequently observed in the cocaine-exposed fetuses, the most common being pulmonary

stenosis, transposition of great vessels, and hemopericardium (96–98). Vascular defects resulting in intra-abdominal or mesenteric arterial hemorrhage and cerebral hematoma were also observed, as well as facial abnormalities such as a cleft lip. These congenital malformations may be the result of hypoperfusion or interruption of blood flow to the developing embryo (see Figure 3) (99,100).

Normal cardiac embryonic development depends on adequate fetal blood flow and myocardial oxygenation. Vasoconstriction secondary to cocaine exposure may lower intracardiac blood flow and thereby interfere with development of specific regions of the heart (101). Cocaine-induced fetal hypoxia may stimulate the release of catecholamines, which promote cardiac hyperplasia and hypertrophy (101). Animal studies demonstrate a wide variety of cardiac anomalies, including pulmonary stenosis, transposition of the great vessels and hemopericardium, and ventricular hypertrophy (96,98). Lipshultz et al. noted that the rate of cardiac defects among neonates who tested positive for cocaine at delivery was significantly higher than that among cocaine negative neonates (relative risk = 3.7; 95% confidence interval) (101). Structural cardiac defects associated with cocaine exposure in human infants include: patent ductus arteriosus, atrial septal defect, ventricular septal defect, pulmonary atresia, hypoplastic heart, ventricular hypertrophy, valvular abnormalities, and aortic valve prolapse (21,100,102–104).

Nonstress testing of cocaine-exposed fetuses reveals slower fluctuations of the fetal heart rate with fewer accelerations than in nonexposed fetuses (105). Cardiac conduction defects, dysrhythmias, voltage abnormalities, and transient ventricular tachycardia have also been reported in cocaine-exposed infants (101,106,107). These rhythm abnormalities may be due to enhanced β-adrenergic stimulation or to a direct toxic effect of cocaine. Increased heart rate and arterial blood pressure have been observed both in animal studies and human infants (108). Van de Bor et al. demonstrated elevated arterial blood pressure by oscillometry and diminished cardiac output and stroke volume assessed by pulsed Doppler echocardiography on the first postnatal day in full-term exposed infants (109). By the second postnatal day, however, these cardiovascular variables were similar in both exposed and nonexposed infants. The authors suggested that elevated norepinephrine levels in the cocaine group on the first postnatal day were responsible for this phenomenon.

Little is known about the relationship between cocaine exposure *in utero* and respiratory distress syndrome in neonates. One preliminary report observed a decreased incidence of respiratory distress syndrome among infants exposed to cocaine prenatally (110). Similarly, accelerated fetal lung maturation has been demonstrated in rabbits after *in utero* exposure to cocaine (111). Other *in vivo* experiments in pregnant rats have shown increased surfactant maturation (112). Cell culture studies, however, suggest no change in the surfactant production (113).

An early retrospective study concluded that sudden infant death syndrome (SIDS) was the cause of death in 10 of 60 infants exposed to cocaine *in utero* (114). However, a large study involving 275 cocaine-exposed infants reported that the risk of SIDS was 5.6/1000 among the exposed infants, as compared to 4.9/1000 among nonexposed infants, a difference that was not significant (115). Most studies suggest a moderately elevated risk of SIDS, but a clear association has not been firmly established (6,116). Pneumocardiograms performed on full-term infants exposed to cocaine reveal a longer duration of apnea and more frequent episodes of bradycardia compared to controls (117).

Manifestations of acute fetal cocaine intoxication include hyperflexion and prolonged periods of scanning eye movements, and followup of these neonates reveals excessive irritability and unexplained tachypnea (118). Chasnoff et al. documented significant differences in neurobehavioral capabilities (orientation, motor ability, alertness, and abnormal reflexes) in cocaine-exposed infants compared to controls (76). Other investigators have described irritability, poor motor function, hypotonia, seizures, and apathy (80,119,120). Fine and gross motor skill delay was documented in children aged 5–30 mo after cocaine exposure during pregnancy (121). *In utero* exposure to cocaine has also been associated with neonatal electroencephalographic (EEG) abnormalities and clinical seizures (119). Although nearly half of the neonates had EEG abnormalities at birth, EEG tracings were normal by age 12 mo. The abnormal EEG, however, did not correlate with the severity of neurologic signs or maternal factors.

Cerebral infarct in a term infant has also been described in association with maternal drug abuse including cocaine (122). Assessment of intracranial pathology by ultrasonography in a group of cocaine-exposed infants revealed multiple abnormalities, including acute infarction, intraventricular hemorrhage, subarachnoid hemorrhage, and white matter densities and cavities (123). The intracranial hemorrhages and ischemic lesions may be secondary to cocaine-induced alterations in cerebral blood flow, which is elevated during the first day of life in cocaine-exposed infants (120,124). Cocaine has also been shown to cause cerebral vasoconstriction in newborn piglets and in cerebral arteries of perinatal lambs (125,126).

Neonatal renal dysfunction has also been reported after *in utero* cocaine exposure. Zilleruelo et al. described persistent hyperchloremic metabolic acidosis in 27% of cocaine-exposed neonates (127). Chasnoff et al. reported the occurrence of prune belly syndrome and hydronephrosis in a group of infants exposed to

cocaine *in utero* (73). Recent studies report a significant association between cocaine use and the risk of urologic defects (128,129). The estimated relative risk is 4.4 for urologic anomalies, including hydronephrosis, prune belly syndrome, urethral and renal agenesis, ambiguous genitalia, and unilateral ectopic fallopian tube (128).

The gastrointestinal tract is also vulnerable to the vasoconstrictive and ischemic sequelae of prenatal cocaine exposure. An association between *in utero* cocaine exposure and necrotizing enterocolitis has been reported (130,131). Jejunal atresia, imperforate anus with midcolonic atresia, anal atresia, and widespread infarction of the bowel have been described as well (69,102,132).

Harris et al. reported a series of 500 term neonates in a well baby nursery, 68 of whom tested positive for cocaine (133). Partial ankyloglossia (fusion of the tongue to the floor of the mouth) and shortened, thickened frenulum restraining tongue mobility were more likely to occur among cocaine-exposed neonates. Short frenulum may affect the transverse and anteroposterior development of the maxilla (133).

Cocaine exposure in neonates can also occur after delivery. Ingestion via breast milk and passive inhalation of free base cocaine have been suggested as possible mechanisms (134,135).

Anesthetic Implications

Given the high incidence of fetal asphyxia, anesthesiologists may be frequently called upon to assist in the resuscitation of these infants. Because many of the exposed mothers and infants will not be identified in a spot urine test, anesthesiologists must have a high index of suspicion for intrauterine cocaine exposure. A history of absence of prenatal care, alcohol use, premature rupture of membranes, and positive syphilis serology should suggest the possibility of maternal cocaine abuse (3,5,9,82). The presence of a known obstetrical complication associated with maternal cocaine abuse (i.e., placental abruption, preterm labor, precipitate delivery, stillbirth) may also indicate cocaine exposure.

Preoperative evaluation of these infants should consider all the reported organ system abnormalities. Physical examination may reveal an irritable infant with poor motor ability, hypotonia, and low birth weight. A careful airway evaluation should be performed with the possibility of partial ankyloglossia in mind. Because of the documented increased rate of cardiac anomalies among these infants, a cardiology consult should be considered. In addition, preoperative electrocardiogram is of special importance because of the cardiac conduction defects, dysrhythmias, and transient ventricular tachycardia that may be associated with intrauterine cocaine exposure (101, 106,107).

In choosing an induction technique, the anesthesiologist should consider the reported elevated arterial blood pressure and diminished cardiac output and stroke volume in the first day of life (109). Elevated catecholamine levels in these infants may lead to dysrhythmias if halothane or local anesthetics with epinephrine are used.

There are no published data regarding anesthetic outcome in cocaine-exposed infants. Because of the increased incidence of SIDS, cocaine-exposed infants should be monitored postoperatively for the possibility of apnea, and, therefore, may not be suitable candidates for outpatient surgery.

Summary

The growing use of cocaine among pregnant women and women of childbearing age has become an issue of great concern to physicians. Cocaine abuse among parturients is associated with multitarget organ involvement, including the cardiovascular, respiratory, neurologic, and hematologic systems. Cocaine use during pregnancy is also an independent contributor to the risk of placental abruption, preterm labor, precipitate delivery, stillbirth, and others. Although a history of premature rupture of membranes, smoking, alcohol use, syphilis serology, and use of other illicit drugs suggests cocaine abuse, the single most important predictor is the absence of prenatal care. The intraoperative anesthetic management should take into consideration the different effects of cocaine on the mother, the fetus, and the neonate.

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