Review article

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THE EFFECTS OF COCAINE ON THE COURSE AND PREGNANCY OUTCOME

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The epidemic of drug addiction is a significant public health issue worldwide. Through easy availability of cocaine its use by childbearing women may have deleterious effects on course and outcome of pregnancy.

Cocaine use during pregnancy causes: intrauterine growth retardation, abruptio of placenta, increased frequency of premature birth, premature rupture of the membranes, precipitous labor, meconium-stained amniotic fluid, stillbirth, neonatal necrotizing enterocolitis, neonatal bowel perforation, complete bilateral absence of the diaphragm, neonatal respiratory disorders, neonatal subcutaneous fat necrosis, sudden infant death syndrome, intimal fibromuscular dysplasia of numerous blood vessels, hearing impairment, retinal hemorrhages, fetal or maternal intracranial accident, rupture of the uterus, ruptured tubal ectopic pregnancy, placenta previa, changes in neonatal behavior, neonatal cardiac arrhythmias, various congenital anomalies, maternal myocardial infarction and long QT interval in a parturient .

Retrospective studies have shown that intrauterine exposure to cocaine causes major malformations in newborns: congenital heart defects, genitourinary, brain and skull anomalies, absence of limbs, ankyloglossia, hypothalamic hamartoblastoma, and Poland-Möbius syndrome.

Some authors suggest that there is a specific fetal cocaine syndrome and a link between the high incidence of autism and exposure to cocaine in utero. Cocaine is a neurobehavioral teratogen, as long-term monitoring of prenatally exposed children has shown deleterious effects of cocaine on their psychophysical development. Cocaine use during pregnancy can result in a wide range of adverse effects on pregnancy and its outcome.

Key words: cocaine, pregnancy, neurobehavioral teratogen, congenital anomalies

Pregledni rad

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EFEKTI KOKAINA NA TOK I ISHOD TRUDNOĆE

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Epidemija zavisnosti od nedozvoljenih droga je značajan problem javnog zdravlja širom sveta. Zahvaljujući lakoj dostupnosti kokaina, njegova upotreba kod žena u fertilnom periodu može imati štetne efekte na tok i ishod trudnoće.

Upotreba kokaina u trudnoći uzrokuje: usporen intrauterini rast ploda, abrupciju placente, povećanu učestalost prevremenog porođaja, prerano

pucanje plodnih ovojnica, prisustvo mekonijuma u amnionskoj tečnosti, mrtvorođenost, neonatalni nekrotizirajući enterokolitis, neonatalnu perforaciju creva, kompletno odsustvo dijafragme, neonatalne respiratorne poremećaje, neonatalnu nekrozu potkožnog masnog tkiva, sindrom iznenadne smrti novorođenčeta, fibromuskularnu displaziju intime brojnih krvnih sudova, oštećenje sluha, krvarenje u mrežnjači, intrakranijalna krvarenja fetusa ili majke, rupturu materice, rupturu jajovoda zbog vanmaternične trudnoće, placentu previu, promene u neonatalnom ponašanju, neonatalne srčane aritmije, različite kongenitalne anomalije, infarkt miokarda trudnice i dug QT interval kod porodilje.

Retrospektivne studije su pokazale da intrauterino izlaganje kokainu izaziva *major* malformacije kod novorođenčadi: urođene srčane mane, anomalije genitourinarnog sistema, mozga i lobanje, odsustvo udova, ankiloglosiju, hamartoblastom hipotalamusa i Poland- Möbius sindrom.

Neki autori sugerišu da postoji specifičan fetalni kokainski sindrom i veza između visoke incidencije autizma i izloženosti kokainu in utero. Kokain je neurobihejvioralni teratogen, jer je dugotrajno praćenje prenatalno izložene dece pokazalo štetne efekte kokaina na njihov psihofizički razvoj.Upotreba kokaina tokom trudnoće može dovesti do širokog spektra štetnih efekata na trudnoću i njen ishod.

Ključne reči: kokain, trudnoća, neurobihejvioralni teratogen, kongenitalne anomalije

Introduction

Cocaine is a local anesthetic, central nervous system stimulant and appetite suppressor. It primarily acts on the presynaptic level by blocking reuptake of monoamine neurotransmitters dopamine, norepinephrine and serotonin through specific plasma membrane transporters. In this way, it causes tachycardia, peripheral vasoconstriction, increase in blood pressure, agitation, euphoria and excitation.

The name of this drug is derived from the word "khoka" meaning "divine tree" in the language of Inca. Cocaine is produced by extraction from evergreen leaves of *Erythroxylum coca* (Bolivian coca) and *Erythroxylum novogranatense v. truxillense* (Peruan coca), as well as other *Erythroxylum* species originating from South America. Spanish conquistadors observed in XVI century that natives could work for days and move without rest and food in the high Andes, when chewing these plants leaves (1).

Cocaine (molecular weight is 303.4) is an ester of benzoic acid and ecgonine aminoacid (methylbenzoylecgonine – $C_{17}H_{21}NO_4$). It is a fine, colorless or white crystalline powder with bitter taste, highly soluble in alcohol and ether (insoluble in water). Cocaine melting point is 96-98°C. About 1 kg of crude cocaine may be produced out of 150 kg of coca leaves. The end-product of coca leaves extraction is 99% cocaine in the form of cocaine hydrochloride. It is often "cut" with other substances of similar color: starch, powder, lactosis, sacharosis, mannitol, lidocaine, procaine and amphetamine. Cocaine hydrochloride – $C_{17}H_{21}NO_4HCl$ (molecular weight is 339,8) is a fine, colorless or white, bitter tasting crystalline powder, highly soluble in water and alcohol, insoluble in ether. Its melting point is 197°C, when it begins to decompose.

From South America and Asia, cocaine is exported world-wide and illegally sold as a white powder of uncertain purity. In the street (illegal) market, cocaine is found in various concentrations (30-60%) and by different names: "c", "charlie". "coconut", "coke", "cola",

"crack", "dust", "ice", "king", "lady", "lady snow", "rock(s)", "snow", "snowflake", "toot", "white", etc.

A large number of people world-wide are using cocaine occasionally or regularly. About 41 million people aged ≥18 years reported lifetime use of cocaine, and 5.4 million people reported having used cocaine in 2019 among hospitalized patients in the United States of America (USA) (2). According to the report by the United Nations Office on Drugs and Crime annual prevalence of cocaine use expressed as a percentage of the population in Serbia (age 15-64) was 2.0% in 2018 (3)

There are various ways to consume cocaine: orally, intranasally, intravenously, by inhaling smoke or rubbing it into mucosas. The slang terms for these are: chewing, draw up, sniffing, smoking, etc. Cocaine is sniffed into nostrils and absorbed through the nasal mucosa. The effects start in 3-5 minutes, and last for 30-60 minutes. Intravenous cocaine application is followed with almost immediate and much stronger effects (in 6-8 seconds) which lasts 10-15 minutes. Cocaine abuse causes severe psychological dependence. Quitting cocaine may lead to occurrence of various withdrawal symptoms: the urge for cocaine, depression, apathy, paranoia, suicidal thoughts, loss of sexual desires, insomnia, etc.

"Crack" is the street name for freebase cocaine produced by mixing powder cocaine hydrochloride with ammoniac or sodium bicarbonate and water, and later by heating it until hydrochloride evaporates. Such a substance has a form of small, wax-colored, hard blobs, and it is ready for smokings. The term "crack" is onomatopoeic, and comes from crackling that can be heard while smoking it. When smoking "crack" euphoria is obtained in less than 10 seconds. Such a quick and powerful effect is the reason for "crack's" popularity during mid-80's of the 20th century. Psychological and physical addiction is developed quickly, sometimes already after the first dose. Long-term "crack" abuse leads to complete degradation, both

psychologically (loss of self-control and self-esteem) and physically. The “crack” addict’s personality is dominated by: depression, extreme mood swings and the feeling of persecution.

In the case of simultaneous cocaine and alcohol abuse, cocaethylene is synthesized in the liver. This metabolite emphasizes euphoric effects of cocaine, but is more toxic and increases the risk of sudden death.

Cocaine addicts usually consume both cocaine and heroin. This combination is called the “speedball” because the effects of these two substances potentiate each other. This is especially dangerous because heroin takes away the unpleasant “edge” effect of cocaine, giving the addict a false sense of security. Therefore, more heroin or cocaine can be taken, which can lead to overdose and a fatal outcome.

Cocaine effects on gestation in animals

Extremely low concentrations of cocaine are detected in fetal tissues after administration to pregnant mice (4). Cocaine application during organogenesis results in the increased frequency of intrauterine resorptions, as well as skeletal defects, exencephaly, eye anomalies, hydronephrosis, criptorchism and delayed ossification of cranial bones and the bones of the paws (5). Administration of prazosin (a selective α1-blocker) reduces, while administration of diltiazem (a calcium channel blocker) increases the incidence of fetal anomalies in the offspring of mice exposed to cocaine in utero (6). In rats, during gestation, cocaine increases the possibility of resorption or fetal edema, and can also cause a significant decrease in fetal weight (7), as well as focal necrosis, necrobiosis, hemorrhages, and inflammatory reactions in the gastrointestinal tract of the embryo (8).

It has been shown that the changes that occur in rat offspring after intrauterine exposure to cocaine (bilateral necrosis and cavitation of the cerebral cortex, hemorrhage and ectopic

outgrowths in the corpus striatum, vacuolization in the lens of the eye) can also be induced by temporary uterine artery occlusion, or directly by pressuring gravid uterus with fingers (9).

Intraperitoneal application of cocaine to pregnant rats during gestation causes dose-dependent development of the fetal soft tissue malformations, predominantly in the genitourinary system (10). Doses corresponding to "recreational" doses taken by humans (0.5-1.0 mg/kg) may cause the following changes in sheep during gestation: increase in maternal blood pressure (32% and 37%, respectively) and fetal blood pressure (12.6%), decrease in uterine blood flow (36% and 42%, respectively), and increase in catecholamine concentrations (210%). The maximum effect is achieved after 15 minutes, with a subsequent rapid decline (11). Intraperitoneal administration of cocaine to female monkeys during the last 165 days of gestation does not cause any changes in the physical development or behavior of the exposed offspring (12).

Cocaine effects on gestation in women

Cocaine is widely distributed throughout the body after administration, and is rapidly metabolized by esterase enzymes in the circulation and in the liver. The main metabolites are benzoylecgonine, ecgonine, ecgonine methyl ester, and norcocaine, which is highly hepatotoxic. There are three different metabolic pathways of cocaine biotransformation: when hydrolyzed by hepatic and plasma esterases, benzoyl group is lost, forming ecgonine methylester (the most important metabolic pathway); spontaneous hydrolysis (probably non-enzymatic) leads to the formation of benzoylecgonine which is then degraded to ecgonine; and by N-demethylation forming norcocaine. Therefore, the most important metabolites of cocaine are ecgonine methylester, benzoylecgonine and ecgonine, all inactive metabolites. Norcocaine is an active metabolite and may have an important role in the acute poisoning with cocaine. In the presence of alcohol, cocaine undergoes a process of transesterification, forming a

psychoactive metabolite, cocaethylene. This metabolite is more toxic than cocaine itself (13). There are great individual differences in cholinesterase activity, which may explain some obscurities in cocaine effects and metabolism. Plasma cholinesterase activity is significantly decreased during pregnancy (14, 15). Fetus has low plasma cholinesterase activity (14) and cocaine is metabolized very slowly in the fetus. By the end of the fourth hour after the use of cocaine, the most of the drug has already been eliminated from plasma, but metabolites (ecgonine methylester, benzoylecgonine and ecgonine) may still be detected even after 144 hours (16). Depending on the liver and kidney function, 1-9% of unmetabolized cocaine (there is more unmetabolized cocaine in acidic urine) and cocaine metabolites may be detected in the urine (17). Unmetabolized cocaine can also be found in saliva, and is eliminated by feces (17, 18). Cocaine crosses the placental barrier and its metabolite norcocaine persists in amniotic fluid for 4-5 days, even when it is undetectable in maternal blood (19). Both cocaine and benzoylcocaine can still be detected in the urine of the newborn after 5 days (20).

The pharmacological effects of cocaine are associated with reduced catecholamine uptake and corresponding activation of the sympathetic nervous system. Chronic excess of circulating catecholamines in the mother who uses cocaine induces downregulation of catecholamine receptors. Vasoconstriction of the uterine and umbilical arteries causes a decrease in the delivery of oxygenated blood to the fetus, followed by hypoxemia, hypertension, and tachycardia.

The etiology of recurrent hypoxic insults to the placenta and fetus in humans lies in cocaine-induced vasoconstriction of the uterine artery (11, 21, 22). The human umbilical artery also shows intense vasoconstriction in vitro in the presence of cocaine, which can be prevented by the administration of diltiazem (23). In vitro, the human placenta increases thromboxane synthesis and decreases prostacyclin production (24). After analysis of 69 placentas from women who used cocaine during pregnancy, its reduction (in size and weight) was evident. In

addition, ablation was observed in 25% of cases, inflammation/infection (41%), ischemic changes (29%), obliteration of the intervillous space (29%), and placental membrane anomalies (16%) (25). Cocaine readily crosses the placental barrier by simple diffusion because it is highly soluble in both water and fat and has a low molecular weight. At physiological pH, cocaine is poorly ionized, but since the pH of fetal blood is lower than that of maternal blood, significantly higher concentrations of cocaine in the fetal circulation can be expected.

Cocaine and its most important metabolite benzoylecgonine have been detected in fetal brain, liver, kidneys, heart, blood and hair. The highest concentrations were found in the liver (as for cocaine), and the brain (as for benzoylecgonine) (26). The cocaine plasma half-life is around 30 to 90 min, but metabolites are present in the urine for a longer period (2 to 5 days). After intravenous application, cocaine elimination halftime is 30-40 minutes, but its metabolites may be detected even after more than a week. Elimination halftime of benzoylecgonine with newborns is 14.6 hours, twice as long as with adults (27). In one case of a mother's severe poisoning, the concentration of this metabolite measured in the newborn, was 41 000 ng/ml (27).

The prevalence of cocaine use during pregnancy varies worldwide. The percentage established were 4.4% (of 353 newborn meconium samples tested) in Barcelona (Spain) (28), 5.3% (of 1625 pregnant women tested) in Toronto, Canada (29), 11.5% (of 1111 anonymous postnatal maternal urine samples from New York (USA) (30). A staggering 13.6% of newborns (966 of 7083 consecutive births) were reported to have suffered from intrauterine cocaine exposure in Oakland, California (31)!

Long-term use cocaine during pregnancy causes (21, 30-128): intrauterine growth retardation (21,30,38-41,45,49,54,56,58,63,75-80,86,87,90,108,110,120), abruptio of placenta (26,33,34,49,54,63,74-77,89), increased frequency of premature birth (21,30,33,34,42,49,54,56,59,63,76,87,90), premature rupture of the membranes

(36,59,63,91,101), precipitous labor (21,63), meconium-stained amniotic fluid (63), stillbirth (37,76), neonatal necrotizing enterocolitis (43,70,71,113), neonatal bowel perforation (56,80,82,112), complete bilateral absence of the diaphragm (105), neonatal respiratory disorders (50), neonatal subcutaneous fat necrosis (102), sudden infant death syndrome (31,34,37,94), intimal fibromuscular dysplasia of numerous blood vessels (122), hearing impairment (46,119), retinal hemorrhages (114,115), fetal or maternal intracranial accident (36,44,48,49,57,69,90,103,109,126), rupture of the uterus (57,95,111,125), ruptured tubal ectopic pregnancy (55), placenta previa (76,107,115), changes in neonatal behavior (34,53,76,98), neonatal cardiac arrhythmias (36,51,56,100,127), various congenital anomalies (32,34,35,38,41,52,56,62,64-68,72,73,80,83-86,89-94,96-99,117-121), maternal myocardial infarction (104,105,129), and long QT interval in a parturient (123).

Retrospective studies have shown that intrauterine exposure to cocaine causes major malformations in newborns with a risk of 8-10% (37,38). Some authors have linked the increasing number of women and men using cocaine occasionally or regularly to an increase in the incidence of congenital heart defects (32,51). Cocaine exposure can lead to the development of congenital cardiovascular (38,56,65-68,89,91,94,120), genitourinary (34,35,41,49,53,65,67,83,92,99,119), brain and skull anomalies (32,64,83,96-98,117), and absence of limbs (73,83,85,86,116,117). Interestingly, the incidence of ankyloglossia in newborns is 3.5 times higher in those exposed prenatally to cocaine (80). A case of a newborn with hypothalamic hamartoblastoma, postaxial polydactyly in both hands and the left foot, and heart defects (Pallister-Hall syndrome) after intrauterine exposure to cocaine, marijuana, and methaqualone has been reported (32). The development of Poland-Möbius syndrome with calcifications in the medulla oblongata and unilateral defects of the right pectoral muscle, thorax, and hand has been described in a newborn exposed to cocaine during the first trimester

of gestation. In addition, central apnea, bilateral cranial nerve palsies, and dysphagia have been reported after birth (130).

Cocaine has been shown to induce bilirubin metabolic pathways, thereby reducing the risk of hyperbilirubinemia in neonates. Bilirubin concentrations in neonates exposed to cocaine in utero are half that of controls (55±26 μmol/L vs. 110±32 μmol/L) (131).

After birth, neonates exposed to cocaine *in utero* may exhibit the following signs: jittery/tremor, high pitched cry, irritability, excessive suck, hyperalertness and autonomic instability (124).

During the first days of a newborn, minute volume and stroke heart volume are decreased, while mean arterial pressure is increased (132). Hypertension or borderline hypertension was observed in 6 of 12 children exposed prenatally to cocaine, without any renal, cardiovascular, or endocrine abnormalities (133).

Mechanism of action of cocaine on fetus

Cocaine impairs neurotransmission in the central nervous system during embryonic development, especially in the first trimester. It can therefore be considered a neurobehavioral teratogen for humans (49). These changes most likely occur in the central dopaminergic system of infants exposed to cocaine *in utero,* since concentrations of homovanillic acid (a major metabolite of dopamine) are significantly reduced in the cerebrospinal fluid (134). High concentrations of the circulating catecholamine precursor dihydroxyphenylalanine, and consequently increased catecholamine activity, have also been found in children exposed prenatally to cocaine. These changes may play an important role in the pathogenesis of neurobehavioral disorders (78).

The pathogenesis of these impairments at the cellular level includes dysfunctional myelination, disrupted dendritic architecture, and synaptic alterations. Prenatal exposure to

cocaine is also associated with disruption of the hypothalamic-pituitary-adrenal axis hormones that mediate neuroendocrine responses (135).

Children exposed prenatally to cocaine have shown specific language and cognitive deficits, and impaired social development (136,137). There is also a significant depression of organizational responses to external stimuli according to the Brazelton scale in such children (34,37), as well as transient electroencephalographic abnormalities (138). Exposed children have a 2.8 times higher risk of showing learning difficulties, compared with unexposed children (139). Prenatal cocaine exposure slows postnatal growth at seven and ten years of age (140) and predicts poorer perceptual reasoning IQ at the age of nine (141).

In a long-term follow-up study of 70 children exposed to cocaine in utero, a number of significant neurodevelopmental abnormalities were reported: delayed speech (94%) and an extremely high incidence of autism (11.4%) (79). The authors suggest that the high incidence of autism is specific to intrauterine cocaine exposure, as it is not observed in those exposed to other opiates or alcohol. They also described various optical anomalies in children exposed to cocaine *in utero* (142-144): frequent refractive errors, optic nerve anomalies, microphthalmia, development of retinopathy, and prolonged eyelid edema. At age 21, young adults who were prenatally exposed to cocaine had lower mean full-scale (83.7 ± 10.4 vs. 87.3 ± 12.5, $p < 0.1$) and perceptual reasoning IQ (87.3 ± 11.5 vs. 91.4 ± 13.9, ($p < 0.02$),), lower high school completion rates (75% vs. 86%, $p < 0.02$), and were slightly more likely to have been on probation than non-cocaine exposed young adults, but did not differ in Verbal IQ, self-reported problematic substance use or incarceration. Young adults with prenatal cocaine exposed in foster/adoptive had similar lower IQ scores but had better verbal skills and high school graduation rates that did not differ from non-cocaine exposed young adults (80.6 vs 86.2%, $p > .05$) (145).

In 1985-1986, the cost of postpartum care in the United States was 5,200$ more for newborns prenatally exposed to cocaine than for babies who were not exposed to cocaine, and included: longer hospital stays (four days more), stay in the special care units, various medical procedures and therapies, etc. (146). In another study, data showed that intrauterine exposure to cocaine or some other illicit drug in 1991-1992 increased hospital stay by seven days and increased costs by $7,731 compared to controls (147). The United States spends about $500 million annually to address this growing and serious problem (1991 data), which means that about 100,000 newborns are exposed to cocaine *in utero* annually (146)!

Exposure to cocaine during the development of the nervous system can lead to permanent changes in brain structure and function and later produce altered responses to environmental or pharmacological challenges (148). Cocaine use during pregnancy has been associated with a higher risk of heart failure 10 years later (149) and may be associated with a risk of cerebrovascular disease and cerebrovascular interventions more than 15 years later (150).

Cocaine exposure of the developing nervous system can result in lasting changes in brain structure and function and later produce altered responses to environmental or pharmacological challenges (148).

Numerous studies suggest that cocaine causes changes in the fetus, which can vary significantly in intensity and frequency, depending on: the amount of cocaine used, duration and timing of exposure during pregnancy, potential interactions with other drugs (e.g. alcohol), habits, as well as the possibility of obtaining and introducing cocaine into the pregnant woman's body.

Identification of “fetal cocaine syndrome” was not possible until recently, unlike the identification of “fetal alcohol syndrome” and “fetal hydantoin syndrome”. However, attempts have been made and the best description of fetal cocaine syndrome that has been achieved

would be: neurological irritability, large fontanelles, prominent glabella, marked periorbital and palpebral edema, low nasal bridge with transverse crease, short nose, lateral soft tissue nasal build-up and small toe-nails (90).

Conclusion

Using cocaine during pregnancy may have deleterious effects on pregnancy and its outcome. It has been suggested that cocaine abuse causes: intrauterine growth retardation with low birth weight and microcephaly, placental ablation, increased frequency of premature delivery, premature rupture of the membranes, stillbirth, neonatal necrotizing enterocolitis, neonatal bowel perforation, neonatal respiratory disorders, neonatal subcutaneous fat necrosis, sudden infant death syndrome, fetal or maternal intracranial accident, ruptured tubal ectopic pregnancy, placenta previa, changes in neonatal behavior, neonatal cardiac arrhythmias, maternal myocardial infarction and various congenital anomalies. It has not been proven that these effects depend on the dose used, the time of exposure, and the simultaneous use of other drugs with cocaine. Some authors suggest that there is a specific fetal cocaine syndrome and a link between the high incidence of autism and exposure to cocaine in utero. Cocaine is a neurobehavioral teratogen, as long-term monitoring of prenatally exposed children has shown deleterious effects of cocaine on their psychophysical development.

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