Cocaine as a Teratogen [1]


Cocaine use by pregnant women has a variety of effects on the embryo and fetus [5], ranging from various gastro-intestinal and cardiac defects to tissue death from insufficient blood supply. Thus, cocaine has been termed a teratogen, or an agent that causes defects in fetuses during prenatal development. Cocaine is one of the most commonly used drugs in the US and it has a history of both medical and illegal recreational use. It is a drug capable of a wide array of effects on physical and mental health. Research on the teratogenic effects of cocaine began in the early 1980s, and in 1985 research on the effects of cocaine on prenatal development gained widespread attention. Since then, numerous studies have contributed to information about the detrimental impacts of maternal cocaine use on embryonic and fetal development.

Cocaine (benzoylmethylecgonine) is an alkaloid or a nitrogen-based natural compound that occurs in the Erythroxylum coca [6] plant, which is endogenous to South America, Mexico, Indonesia, and the West Indies. Chemist Friedrich Gaedcke, in Germany, isolated the cocaine alkaloid in 1855. Isolation of the compound led people in countries including Germany, Austria, Italy, and the US to the discover and experiment with cocaine's stimulating and anesthetic properties. In the US, cocaine was presented as a drug with potential local anesthetic properties and was first sold in 1885 by the drug company Parke, Davis and Company, in Detroit, Michigan. The drug was sold in the US as an over-the-counter painkiller and antidepressant until 17 December 1914, when the US Congress passed the Harrison Narcotics Tax Act. The Act required that cocaine and other narcotics be regulated and dispensed only with a physician's order. The Harrison Narcotics Tax Act passed partly as a result of The 1912 Hague International Opium Convention, held in The Hague, Netherlands. Representatives from twelve countries convened in The Hague starting 1 December 1911 to create the first international drug treaty, which controlled access to opium, heroin, and cocaine. Signed on 23 January 1912, the treaty required parties to create and enact laws and regulations for the control of those drugs. Despite these regulations, cocaine reemerged as a popular drug in the US in the 1960s. Under the Controlled Substances Act of 1970, the US Congress limited public use of cocaine and categorized cocaine as a Schedule II controlled substance, which would only be dispensed for medical use with severe restrictions.


Cocaine exists in at least two general forms: cocaine hydrochloride and pure cocaine alkaloid or crack cocaine. Cocaine hydrochloride, made by dissolving cocaine in hydrochloric acid, is a water-soluble salt which is often mixed with other substances to modify the drug’s effects. Cocaine hydrochloride is usually sold as a crystalline powder that is taken intravenously or intranasally. Crack cocaine, the second form, is created by mixing cocaine with either ammonia or sodium bicarbonate with water and then heating the mixture. Crack cocaine is water-insoluble and is smoked, spreading more rapidly in the human body than cocaine hydrochloride.

Cocaine works as a central nervous system [14] stimulant by interfering with the nervous cells' reuptake of norepinephrine and dopamine, which are chemicals involved in the transmission of neurological signals, or neurotransmitters; slowed reuptake causes levels of such neurotransmitters to increase in the user. Dopamine accumulation leads to a sense of ecstasy, increased alertness and energy, heightened sexual stimulation, and reduced fatigue. At the same time, increased levels of norepinephrine enables cocaine to accumulate at nerve terminals, which in pregnant women results in the constriction of maternal blood vessels (vasoconstriction) and in high blood pressure (hypertension) at the site where the uterus [10] and placenta [9] attach together. This disruption of blood flow to the uterus [10] and placenta [9] may also result in maternal tachycardia, a condition that manifests in an abnormally high heart rate, an increased risk for ventricular arrhythmias, and amnion [15] rupture, which in turn causes limb defects in the fetus [5].

The injection and inhalation of cocaine by a pregnant woman increases the general toxicity of the drug, as serum cholinesterases, which are partially responsible for cocaine degradation, are diminished in maternal blood serum during pregnancy [8]. An equal dose of cocaine in a non-pregnant woman exerts an elevated and prolonged level in a pregnant woman.
Cocaine use during pregnancy increases the risk of numerous obstetric complications such as spontaneous abortion, uterine rupture, and premature labor and delivery. Additionally, maternal cocaine use can cause abruptio placentae and stillbirth, the death of a fetus in the uterus. These complications result from the constriction of blood vessels in placentas and the resultant decrease in oxygen supplied to the fetus, a state that increases the pregnant woman's blood pressure, thereby increasing uterine activity. This chain of events indirectly results in fetal anomalies such as oxygen deficiency in the fetal tissues (fetal hypoxemia) and bleeding within the fetus's skull (fetal intracranial hemorrhage). Furthermore, cocaine's low molecular weight and hydrophilic and lipophilic nature allows it to easily cross the placenta and enter the fetus, thereby having additional direct effects on fetal circulation.

Restriction of fetal circulation can have a variety of effects on the development of organs or of other anatomy. Some of the common teratogenic defects of cocaine seen in both human and animal fetuses include: the death of parts of the brain and intestine due to insufficient blood supply, swelling of a kidney due to urine backup (hydronephrosis), a variety of cephalic and cardiac disorders, cleft palate, cleft lip, possessing an abnormal number of digits (polydactyly), Down syndrome (Trisomy 21), obstructive genitourinary defects, and gastroschisis, which is when a fetus's intestines stick out of his or her body.

According to a 1996 report from the US National Pregnancy and Health Survey, approximately 45,000 infants born each year in the US have been prenatally exposed to cocaine. Cocaine is one of the most widely used illicit substances among pregnant women. Aside from the known risks associated with cocaine use in general and the complications that arise from cocaine use by pregnant women, cocaine is detrimental to the developing fetus due to the slow rate at which fetuses metabolize cocaine. Exposure to cocaine is thus prolonged in the fetus, making the drug's effects more pronounced and increasing the odds of teratogenic malformations. Additional research on guinea pigs shows that cocaine transfers from pregnant females to fetuses not only via diffusion into the umbilical cord and within the placental blood vessels, but also in the amniotic fluid, suggesting that the fetus may ingest cocaine when it consumes amniotic fluid.

Embryos develop rapidly in early pregnancy, a period in which using teratogenic substances causes the most developmental problems. Specifically, use of teratogenic substances has the greatest effects on fetuses between the third and eighth weeks of human gestation. Studies on rats indicate that embryonic exposure to cocaine inhibits the differentiation of cells into more functional and distinct forms of neural cells.

Maternal cocaine use can lead to severe neurological impairments in offspring. When exposed to cocaine as fetuses, children in early infancy exhibit signs of irritability and hypertonia, a condition in which the central nervous system reduces the ability of a muscle to stretch. Maternal cocaine use can impair the growth of an offspring's brain during both embryonic and fetal development. Early exposure to cocaine and resultant interference with neurotransmitters, which are chemicals involved in attention and arousal, have been shown to cause children to suffer from a lack of attention span and from the loss of visual memories. While studies of the long-term effects of prenatal cocaine exposure are limited, some research supports a link between fetal exposure to cocaine and inattentiveness in mature children. Children exposed to cocaine score lower on intelligence tests than those in control groups, indicating possible reduced intellectual capability in children whose mothers used cocaine during pregnancy.

Research on cocaine's effects on the development of fetal brains indicates that cocaine inactivates cyclin A, a protein that regulates cell division. The inactivation of cyclin A prevents the development of nerve cells in the fetus. To preemptively treat fetuses exposed to cocaine, doctors sometimes prescribe to pregnant women the drug cimetidine, which is usually used to decrease the secretion of stomach acids, but which also restricts the enzymes that metabolize cocaine. Some evidence indicates that cimetidine may reduce fetal exposure to cocaine and potentially preserve normal fetal brain development.

Other physical effects of prenatal exposure to cocaine occur as a result of maternal malnutrition. Pregnant women who routinely use cocaine are often underweight because cocaine is an anorectic, an appetite-decreasing substance. The lack of maternal nutrition can cause the fetus to underdevelop, and it may retard growth of the brain and skull, a disorder known as microcephaly. Children exposed to cocaine as fetuses respond poorly to environmental stimuli compared to children not exposed to cocaine as fetuses. Cocaine-affected infants may also weigh less than the tenth percentile of infants for their age.

Women who use cocaine during their pregnancies sometimes use other illegal substances during the same time period. Furthermore, women who use cocaine during their pregnancy often face greater than normal environmental risks, such as poor to nonexistent prenatal care. Given those factors, researchers can struggle to identify the problems with fetal development due to cocaine alone, and not to other drugs, environmental factors, or mixtures of the three. Regardless of these struggles, much research shows that consumption of cocaine during pregnancy risks the developing embryo and fetus, and that higher levels of exposure lead to increased rates of abnormalities. Cocaine's teratogenicity also plays a role in a number of legal, political, and ethical debates, such as the concerns of taking punitive measures against pregnant women who use the drug. Cases in the US such as Whitner v. State of South Carolina (1997) and Ferguson v. City of Charleston, South Carolina (2001) highlight issues of pregnant women's autonomy versus the protection of fetuses from cocaine's teratogenic effects.

Sources
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