

Cocaine as a Teratogen

Cocaine use by pregnant women has a variety of effects on the embryo and fetus, 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* 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 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.

Research on the teratogenic effects of cocaine began in the early 1980s. In a June 1980 article titled "Teratogenic Potential of Cocaine Hydrochloride in CF-1 Mice," Michael Mahalik, Ronald Gautieri, and David Mann Jr., at Temple University in Philadelphia, Pennsylvania, reported cocaine's teratogenic potential as demonstrated by an array of congenital malformations that occur in the offspring of pregnant mice given 60 milligrams of cocaine per kilogram of mouse tissue. In 1983 David Acker, Benjamin Sachs, Kevin Tracey, and W.E. Wise, all in the US, drew attention to the possible link between maternal cocaine use during pregnancy and abruptio placentae, a separation of the placenta from the uterus during pregnancy. In 1985, Ira Chasnoff, from Northwestern Memorial Hospital in Chicago, Illinois, and William Burns, S. H. Schnoll, and Kayreen Burns, from Northwestern University in Chicago received US national attention on the issue of cocaine's teratogenicity in humans as a result of their article "Cocaine Use in Pregnancy." In the article, the authors discuss a study that compared twenty-three cocaine-exposed pregnancies with drug-free pregnancies. Cocaine users had a higher frequency of spontaneous abortion and their offspring displayed abnormal neonatal behavior as measured by the Neonatal Behavioral Assessment Scale.

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 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 and placenta attach together. This disruption of blood flow to the uterus and placenta may also result in maternal tachycardia, a condition that manifests in an abnormally high heart rate, an increased risk for ventricular arrhythmias, and amnion rupture, which in turn causes limb defects in the fetus.

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. 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, or the specialization, 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

1. Acker, David, Benjamin P. Sachs, Kevin J. Tracey, and W.E. Wise. "Abruptio Placentae Associated with Cocaine Use." *American Journal of Obstetrics and Gynecology* 146 (1983): 220-1.
2. Albertson, Timothy E., William F. Walby, and Robert W. Derlet. "Stimulant-Induced Pulmonary Toxicity." *Chest* 108 (1995): 1140-9.
3. American Society of International Law. "The Second International Opium Conference." *American Journal of International Law* 7 (1913): 838-847.
4. Beeker, Kelly, Carlton Smith, and Sam Pennington. "Effect of Cocaine, Ethanol or Nicotine on Ornithine Decarboxylase Activity in Early Chick Embryo Brain." *Developmental Brain Research* 69 (1992): 51-7.
5. Chang-Tze Yu, Ricky, Te-Chang Lee, T.C. Wang, and Jih-Heng Li. "General Toxicity of Cocaine." *Carcinogenesis* 20 (1999): 1193-9.
6. Chasnoff, Ira J., William J. Burns, S.H. Schnoll, and Kayreen A. Burns. "Cocaine Use in Pregnancy." *The New England Journal of Medicine* 313 (1985): 666-9.
7. Chiriboga, Claudia A., Louise Kuhn, and Gail A. Wasserman. "Prenatal Cocaine Exposures and Dose-Related Cocaine Effects on Infant Tone and Behavior." *Neurotoxicology and Teratology* 29 (2007): 323-30.
8. Coles, Claire D., Kathleen A. Platzman, Iris Smith, Mark E. James, and Arthur Falek. "Effects of Cocaine and Alcohol Use in Pregnancy on Neonatal Growth and Neurobehavioral Status."

- Neurotoxicology and Teratology 14 (1992): 23-33.
9. Controlled Substances Act of 1970, 21 USC § 801 (1970).
 10. Forrester, Mathias B. and Ruth D. Merz. "Risk of Selected Birth Defects with Prenatal Illicit Drug Use, Hawaii, 1986-2002." *Journal of Toxicology and Environmental Health, Part A* 70 (2007): 7-18.
 11. Fromberg, Erik. "Cocaine and Pregnancy, Hype or Science? A Review of the Literature." International Substance Use Library. <http://www.drugtext.org/Cocaine-crack-and-base/cocaine-and-pregnancy-hype-or-science.html> (Accessed May 17, 2013).
 12. *Ferguson v. City of Charleston*. 532 U.S. 67 (2001). <http://www.law.cornell.edu/supct/html/99-936.ZS.html> (Accessed May 17, 2013).
 13. Goldstein, Rachel A., Carol DesLauriers, and Anthony M. Burda. "Cocaine: History, Social Implications, and Toxicity—A Review." *Disease-a-Month* 55 (2009): 6-38.
 14. Hadeed, Anthony J. and Sharon R. Siegel. "Maternal Cocaine Use During Pregnancy: Effect on the Newborn Infant." *Pediatrics* 84 (1989): 205-10.
 15. Hannig, Vickie L. and John A. Phillips III. "Maternal Cocaine Abuse and Fetal Anomalies: Evidence for Teratogenic Effects of Cocaine." *Southern Medical Journal* 84 (1991): 498-9.
 16. Harrison Narcotics Drug Act of 1914. 38 Stat. at L. 785, chap. 1, Comp. Stat. (1916, 6287h).
 17. Hoyme, H. Eugene, Kenneth Lyons Jones, Suzanne D. Dixon, Tamison Jewett, James W. Hanson, Luther K. Robinson, Michal E. Msall, and Judith E. Allanson. "Prenatal Cocaine Exposure and Fetal Vascular Disruption." *Pediatrics* 85 (1990): 743-7.
 18. Hutchings, Donald E., Theresa A. Fico, and Diana L. Dow-Edwards. "Prenatal Cocaine: Maternal Toxicity, Fetal Effects and Locomotor Activity in Rat Offspring." *Neurotoxicology and Teratology* 11 (1989): 65-9.
 19. Lee, Chun-Ting, Jia Chen, Teruo Hayashi, Shang-Yi Tsai, Joseph F. Sanchez, Stacie L. Errico, Rose Amable, Tsung-Ping Su, Ross H. Lowe, Marilyn A. Huestis, James Shen, Kevin G. Becker, Herbert M. Geller, and William J. Freed. "A Mechanism for the Inhibition of Neural Progenitor Cell Proliferation by Cocaine." *PLoS Medicine* 5 (2008): e117. doi:10.1371/journal.pmed.0050117 <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0050117> (Accessed October 16, 2013).
 20. Mahalik, Michael P., Ronald F. Gautieri, and David E. Mann Jr. "Teratogenic Potential of Cocaine Hydrochloride in CF-1 Mice." *Journal of Pharmaceutical Sciences* 69 (1980): 703-6.
 21. McLaughlin, Gerald T. "Cocaine: The History and Regulation of a Dangerous Drug." *Cornell Law Review* 58 (1972-1973): 537-73.
 22. Musto, David F. "America's First Cocaine Epidemic." *The Wilson Quarterly* 13 (1989): 59-64.
 23. National Institute on Drug Abuse. "Commonly Abused Drugs Chart." US National Institutes of Health. <http://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs/commonly-abused-drugs-chart> (Accessed May 17, 2013).
 24. National Institute on Drug Abuse. "What is Cocaine?" US National Institutes of Health. <http://www.drugabuse.gov/publications/research-reports/cocaine-abuse-addiction/what-cocaine> (Accessed May 17, 2013).
 25. Plessinger, Mark A. and James R. Woods Jr. "Cocaine in Pregnancy: Recent Data on Maternal and Fetal Risks." *Obstetrics and Gynecology Clinics of North America* 25 (1998): 99-118.
 26. Rizk, Botros, Jana L. Atterbury, and Lynn J. Groome. "Reproductive Risks of Cocaine." *Human Reproduction Update* 2 (1996): 43-55.
 27. Ryan, Lynn, Sandra Ehrlich, and Loretta Finnegan. "Cocaine Abuse in Pregnancy: Effects on the Fetus and Newborn." *Neurotoxicology and Teratology* 9 (1987): 295-99.
 28. Schiller, Cassandra and Pat Jackson Allen. "Follow-Up of Infants Prenatally Exposed to Cocaine." *Pediatric Nursing* 31 (2005): 427-36.
 29. Singer, Lynn T., Laurie J. Eisengart, Sonia Minnes, Julia Noland, Arthur Jey, Courtney Lane, and Meeyoung O. Min. "Prenatal Cocaine Exposure and Infant Cognition." *Infant Behavior and Development* 28 (2005): 431-44.
 30. Snodgrass, Samuel Robert. "Cocaine Babies: A Result of Multiple Teratogenic Influences." *Journal of Child Neurology* 9 (1994): 227-33.
 31. Strathearn, Lane and Linda C. Mayes. "Cocaine Addiction in Mothers: Potential Effects on Maternal Care and Infant Development." *Annals of the New York Academy of Sciences* 1187 (2010): 172-83.

32. US Department of Health and Human Services, National Institute on Drug Abuse. "National Pregnancy and Health Survey: Drug Use Among Women Delivering Live Births: 1992." Bethesda, MD: National Institutes of Health, 1996.
33. United Nations Office on Drugs and Crime. "The 1912 Hague International Opium Convention." United Nations Office on Drugs and Crime. <http://www.unodc.org/unodc/en/frontpage/the-1912-hague-international-opium-convention.html> (Accessed June 13, 2012).
34. Volpe, Joseph J. "Effect of Cocaine Use on the Fetus." *New England Journal of Medicine* 327 (1992): 399-407.
35. *Whitner v. State*. 492 S.E. 2d 777 (S.C. 1997). <http://faculty.law.miami.edu/zfenton/documents/Whitnerv.State.pdf> (Accessed May 17, 2013).