PRENATAL EXPOSURE TO AMPHETAMINES

Risks and Adverse Outcomes in Pregnancy

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When an adverse pregnancy outcome occurs, one considers the prenatal factors that may have contributed to the outcome. When drugs such as cocaine and amphetamines are discovered to be associated with the pregnancy, the infant frequently is labeled as a "cocaine baby," "crack baby," or "speed baby." Such infants carry these distinctions for life and are expected to have behavioral deficiencies and learning disabilities that will never be overcome because of the "teratogenic exposure it received in utero." Despite the fact that many women who use cocaine or amphetamines during pregnancy deliver normal infants developing within normal parameters, there are many maternal and fetal risks associated with the use of cocaine or amphetamines during pregnancy. This article reviews the effects of amphetamines on pregnancy and their respective effects on the fetus.

Often, the effects of cocaine and amphetamines are considered to be identical, because both drugs have essentially similar pharmacologic effects as central nervous system (CNS) stimulants. However, as demonstrated in this review, these compounds produce different developmental effects as well. This article reviews the background effects of amphetamines, their respective effects on human pregnancy, and the effects demonstrated in animal studies.

Several components of prenatal drug abuse in humans may affect the fetus or newborn. The following text outlines those described by

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Brooks-Gunn and co-workers[8]; several others are added for completeness. The first component is the drug effect on the developing neural system. The second component is drug exposure resulting in prematurity and fetal growth retardation. The third involves exposures of the drug after birth occurring via passive inhalation and breast-feeding. The fourth involves characteristics of the mother, including other abused drugs such as alcohol and nicotine, education, and mental health. The fifth mechanism focuses on how the affected child influences the behavior of its mother, that is, a drug-abusing mother may not care for her premature or low-birth-weight infant in the same manner as a drug-free mother. The sixth and final mechanism outlined by Brooks-Gunn and colleagues is the social environment in which the child is raised. All of these mechanisms are important factors contributing to the development of the prenatally drug-exposed child.

Several other issues must be considered in a discussion of drug abuse in pregnancy. One of these is the gestational period in which the drug exposure occurs, because damage to structures occurs at critical developmental time windows. Toxicologic issues are also important and involve exposure concentration of the drug and how the drug is handled by the body. Because drug disappearance depends on metabolic machinery and enzymatic capability, the toxicity and thus teratogenicity of a drug are likewise dependent on such enzymatic capacity. In both the fetus and the mother, the genetic composition that determines this enzymatic capacity influences and defines the concentration of the drug at the critical fetal site of action. If drug concentrations exceed the effect threshold, damage may occur.

The fact that a woman takes a drug during pregnancy does not mean she will deliver a malformed infant or behaviorally compromised child, because cause and effect are not always clearly defined. Malformations and behavioral effects in humans are not all-or-none phenomena, and whether damage occurs depends upon a multitude of different factors, including environmental, nutritional, genetic differences, and polydrug abuse. It can be concluded, however, that the use of certain drugs during pregnancy will increase the *risks* of adverse outcomes.

AMPHETAMINES: STRUCTURAL-ACTIVITY RELATIONSHIPS

Amphetamines can be considered noncatecholamine sympathomimetics, because they lack catecholamine structure yet have sympathomimetic actions. Amphetamine resembles the sympathetic neurotransmitter, norepinephrine, with one exception in that it has no hydroxyl groups at the 3′, 4′ positions on the benzene ring (Fig. 1). Because the enzyme catechol-O-methyl-transferase (COMT) utilizes the 3′,4′-dihydroxy–substituted aromatic ring (catechol) as substrate, COMT is one of the major pathways in inactivating released norepinephrine at nerve terminals. Because amphetamine lacks this catechol structure, COMT is inef-

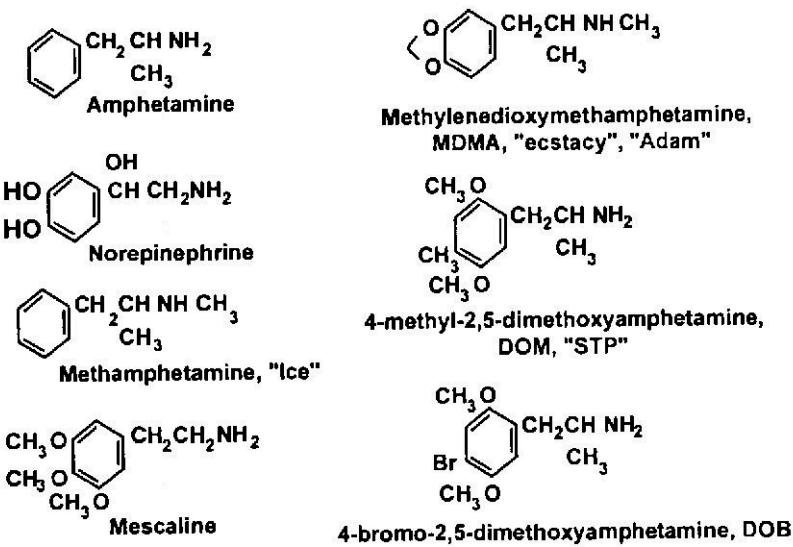

Figure 1. Norepinephrine, amphetamine, and analogues.

fective in metabolism of amphetamines. Amphetamines also differ from norepinephrine by the substitution of a methyl group on the alpha carbon of the nitrogen and by the lack of a hydroxyl group on the beta carbon. The lack of hydroxyl groups confers the lipophilic nature and thus readily explains the distribution of amphetamine into the CNS. The presence of the methyl group on the alpha carbon prevents metabolism by monoamine oxidases (MAO), the other major metabolic pathway for inactivating norepinephrine. The structural characteristics described above account for the wide distribution and long duration of action of amphetamine, the effects of which can last for as many as 10 to 12 hours.

Amphetamine produces four primary effects that are dependent on the dose administered. The primary effect of amphetamine is stimulation of the CNS, producing increased alertness, decreased fatigue, sleeplessness, euphoria, and exhilaration. The mechanism by which amphetamines are thought to produce their CNS effects is by the release of norepinephrine from noradrenergic CNS neurons. Amphetamines are considered to have weak direct actions at alpha receptors because of the lack of hydroxyl groups on the alpha and beta carbons, and the fact that further substitutions on the amino group reduce the sympathomimetic effects of amphetamines. However, because the effect of amphetamine is to release stored norepinephrine in the CNS, it may be difficult to distinguish which responses are caused by the direct effects of amphetamines and which are indirect effects of increasing systemic levels of norepinephrine or other neurotransmitters, such as dopamine and serotonin, by their release into the blood vascular system. The systemic

effects of amphetamines (second primary effects) are hypertension, dilated pupils, tremors, and hyperactivity.

Because cocaine also acts as a CNS stimulant, both cocaine and amphetamines have the same action in that they both affect norepinephrine metabolism, although they accomplish this by different mechanisms. Cocaine inhibits the reuptake of released norepinephrine. The increased norepinephrine at the nerve terminals diffuses into the blood vascular system to circulate to other regions to produce vasoconstriction. In terms of subjective effects (third primary effects), cocaine users cannot distinguish their subjective reactions to cocaine or amphetamines, because intravenous administration of 16 mg of cocaine is indistinguishable from administration of 10 mg of amphetamine.[20] At higher doses, amphetamines release serotonin from central serotonin neurons or directly interact with central serotonin receptors. This interaction with serotonin receptors may explain some of the hallucinogenic effects of amphetamines of "visualizing sounds" and "hearing colors." The fourth primary effect of amphetamines is the production of anorexic effects and a suppressed appetite, although this effect exhibits tolerance with chronic administration. Derivatives such as phenylpropanolamine are being used as appetite suppressants in many over-the-counter diet control medications. Toxic effects of amphetamines are seen at even higher doses and involve many of the characteristics seen with cocaine overdoses—hypertension, retinal damage, cardiac arrhythmias, hyperthermia, seizures, shock, stroke, and death.[9] Increased toxicity is seen at lower concentrations of amphetamines in patients receiving MAO inhibitors and may indicate a reduced capacity to handle an increased norepinephrine challenge.[27]

The dosages of amphetamines used vary and are dependent on the route of administration and the individual subject. Oral dosing reaches peak serum levels by 1 to 2 hours after ingestion, and subjective effects can be achieved with oral dosages of as low as 10 mg. Amphetamine addicts usually ingest 200 mg first, with 300 to 3000 mg injected intravenously every 2 hours. An experienced "speed" addict can reach a total daily intake of 30,000 mg or more.[43] Correlation of prenatal exposures or street exposures with amphetamine doses that produce effects in animal paradigms is complicated by this enormous range of possible doses. An estimate can be made based on typical doses of methamphetamines in novice users, ranging from 60 to 100 mg.[23] For a 50-kg woman, this dose would correlate with 1.2 to 2.0 mg/kg administration.

There are several amphetamines, having different structural and activity relationships. Because of the hydroxyl group on the alpha carbon of the side chain of amphetamine, both *d* and *l* isomers exist. The *d* isomer confers a four times greater CNS effect than the *l* isomer. This characteristic was first emphasized with the availability of the dextroamphetamine nasal decongestant, Dexedrine, in the 1930s. The *l* isomer has greater systemic effects than the *d* isomer, and the racemic mixture is marketed as Benzedrine. These trade names account for the street nicknames of "dexies" and "bennies." Methamphetamine or "ice" is N-

methylated amphetamine and is a favorite of abusers because it can be readily dissolved in water for parenteral administration via injection or can be smoked.

Substitution of aryloxy groups on the benzene ring produces "designer drugs," which are some of the most powerful psychostimulants available. The natural psychostimulant mescaline is derived from the peyote cactus. Its chemical structure, 3,4,5,methoxyphenylethylamine, closely resembles both norepinephrine and amphetamine (see Fig. 1). Not surprisingly, 3,4,5,trimethoxyamphetamine (TMA) resembles mescaline and is more potent. One danger of TMA is the small difference in dose between its desired psychoactive effects and toxicity.[9] The most potent methoxysubstituted psychostimulant is 2,5-dimethoxy-4-methylamphetamine or "STP" (serenity, tranquillity, and peace). Other designer amphetamines include 4-methyl-2,5,dimethoxyamphetamine (DOM); 4-bromo-2,5,-dimethoxyamphetamine (DOB), methylenedioxyamphetamine (MDA); methylenedioxymethamphetamine (MDMA), known as "ecstasy" or "Adam"; methylenedioxyethamphetamine (MDEA) known as "Eve"; and methcathinone. The reader is referred elsewhere for descriptions of these drugs.[9]

Concerning the metabolism of amphetamines, approximately half of the systemic load is metabolized by aromatic hydroxylation, deamination, and N-conjugation, which makes the parent compounds more polar and thus readily excreted. The remaining half is excreted unchanged, and an acid urine increases excretion. Substitution of the aromatic ring at the 4′ position prevents aromatic hydroxylation, thus increasing the efficacy of any amphetamine derivative with this characteristic. Various animal species metabolize amphetamine differently, a fact that should be kept in mind when interpreting results. For example, amphetamines are biotransformed by rats by aromatic hydroxylation, whereas rabbits metabolize amphetamines by deamination.[65]

MATERNAL EFFECTS OF AMPHETAMINES IN PREGNANCY—HUMAN DATA

Little documentation exists regarding the effects of amphetamines in pregnant women, because attention for the most part has focused on their effects in the fetus. In a study of 53 amphetamine-addicted women who used the drug throughout pregnancy, maternal hypertension, tachycardia, proteinuria, prematurity, premature labor, and placental hemorrhage[18, 52] were the most common maternal complications. Because both amphetamines and cocaine increase systemic norepinephrine levels, the effects of maternal hypertension and maternal tachycardia are not surprising. However, one of the frequently reported toxic effects of amphetamine use is conspicuously absent from any descriptions of maternal effects of amphetamine use during pregnancy. In the nonpregnant state (and in men), common sequelae of amphetamine abuse are cerebrovascular accidents, cerebral hemorrhages, and strokes.[15, 25, 28, 57, 58]

In the literature describing the use of amphetamines during pregnancy, there are no case studies of cerebrovascular accidents occurring in pregnant women.

In contrast, several reports involving cocaine use have cited the occurrence of subarachnoid and intracerebral hemorrhage after maternal cocaine ingestion.[34, 38] It is not clear why a common toxicity characteristic of amphetamine use in nonpregnant subjects and a demonstrated characteristic of cocaine use in pregnancy are notably absent from case studies of pregnant amphetamine users. Either these maternal characteristics have not been reported when they have occurred, or they simply do not occur. In view of the toxic effect of amphetamines to produce cerebrovascular accidents in the nonpregnant population, it can be speculated that pregnant women may titrate their dosages because of possibly enhanced CNS effects with pregnancy, or that pregnancy may somehow protect the brain from damaging cerebrovascular injuries.

In studies of the prenatal effects of amphetamines used during pregnancy, exposure data for both amphetamine (and methamphetamine) and cocaine are often combined, because both compounds are CNS stimulants. When these prenatal effects are reported clinically, there are no statistical differences between amphetamine and cocaine groups, whereas both groups differ from appropriate controls. Also, little distinction is made in these reports with regard to the form of amphetamine used during pregnancy, although usually methamphetamine is the most common choice among intravenous drug users.

Detailing the effects of the different types of amphetamines used during pregnancy is an important issue that has not been addressed completely with regard to fetal outcome. These issues warrant further investigation into the postnatal and adolescent periods. Even less is known about the prenatal effects of designer drugs, which are modified amphetamines. Amphetamines and methamphetamines can be categorized as having teratogenic effects (malformations), systemic effects (transient effects that subside after elimination of the drug), and behavioral effects in infants and newborns. Most of these sequelae have been demonstrated in animal studies and are described in greater detail in the following sections.

FETAL EFFECTS OF AMPHETAMINES IN PREGNANCY—HUMAN DATA

Malformations and adverse outcomes reported with the use of amphetamine or methamphetamine during pregnancy include cleft lip,[35, 42, 47, 61, 67] cardiac defects,[35, 47, 48, 51] low birth weight,[35, 52] growth reduction,[18, 35, 52] reduced head circumference,[18, 35, 52] biliary atresia,[22, 33] prematurity,[17] stillbirth,[17] hyperbilirubinemia requiring exchange transfusion,[17] cerebral hemorrhage,[16] low body fat,[35] mongolian spots,[35] systolic murmur,[35] and undescended testes.[35]

The reported malformations are those *associated* with amphetamine

use during pregnancy. Whether these defects are related to the effects of amphetamine or are caused by the environment of the drug user or by other extraneous factors remains to be defined. The association becomes better defined by the number of reports demonstrating similar findings in different populations. Interestingly, the pattern of malformations seems to differ from that reported with cocaine use. Cleft lip and palate have not been reported with prenatal cocaine use but have been cited in five reports of amphetamine use during pregnancy. Moreover, in one report, three infants with oral clefts were known to be exposed to amphetamines on days 43, 50, and 50 of gestation, which is within the crucial period of oral facial development.[42] Clefting was associated with amphetamine use during pregnancy in 3 of 11 cases reported in poly-drug-exposed infants in Australia. The author observed that the presence of these defects was associated with exposure to amphetamine before 7 weeks' gestation.[67] Cardiac defects have been reported with cocaine exposure; however, there seems to be a greater incidence of cardiac anomalies with amphetamine exposure. Nora and co-workers[50] were among the first to report the fetal cardiac malformations with prenatal amphetamine exposure. These investigators demonstrated an increased rate of transposition of the great vessels in humans and subsequently studied the cardiac and other effects of prenatal amphetamine exposure in greater detail in murine models. Other investigators have cited major cardiac anomalies, including double aortic arch,[18] atrial-septal defect, and atrioventricular canal defect.[21] Amphetamine-related consequences, including fetal growth restriction, reduced head circumference, low birth weight, and cerebral hemorrhages, have also been reported with prenatal cocaine exposure and are most likely related to the ability of amphetamine (and cocaine) to produce vasoconstriction via increasing circulating levels of norepinephrine and other vasoactive amines (serotonin and dopamine). These vasoconstrictive effects restrict nutrient delivery to the developing fetus and could also be related to, or enhanced by, the anorectic effect of amphetamine as an appetite suppressant.

Systemic effects seen in the newborn with amphetamine or methamphetamine use during pregnancy include bradycardia and tachycardia.[52] Most of these cardiovascular effects resolve, presumably after the drug has been eliminated, or when alterations in norepinephrine metabolism have recovered.

However, visual cognitive effects and changes in behavior seem to be permanent.[24] Hansen and co-workers[24] examined children exposed during pregnancy to amphetamine, cocaine, or a combination of both. The infants prenatally exposed to drugs were tested at 4.5 months using the visually evoked potential (VEP), which is an averaged evoked potential demonstrating visual function from the retina to the visual cortex. Subsequently, the infants were tested between 6 and 12 months of age using the Fagan test of infant intelligence (FTII). VEP latencies and amplitude characteristics were not different between the different groups. The drug-exposed infants, however, performed worse on the visual recognition test (FTII). These data demonstrate that exposure to

amphetamines, cocaine, or both did not alter the neurologic transmission of the visual tracts, but that the drugs did alter memory or other intelligence factors in the processing of those signals within the cerebral cortex. One limitation in interpreting the data is that drug exposure may have merely imparted a developmental delay rather than a permanent early learning disability. Similar studies of these infants performed later in the toddler stage and during adolescent life would clarify these issues and would determine whether the impaired intelligence seen earlier is permanent or is a developmental delay from which the infants can recover.

Short-term legalization of drugs of abuse occurred in Sweden during the 1960s. The resulting retrospective and prospective populations of children prenatally exposed to amphetamines were monitored for their progress and performance. In the years that followed, several reports demonstrated that prenatal exposure to amphetamines resulted in altered growth and behavior. In studies of virtually the same group of children as neonates, at 8 years of age, and at 14 years of age, a larger number of amphetamine-exposed children were retained from grade advancement and lagged behind in mathematics, language, and physical training in comparison with unexposed controls.[13, 17, 18] When these children were 14 years of age and past puberty, surprising and striking sex differences were observed with respect to growth.[13] Drug-exposed boys were taller and heavier in weight than two Swedish standards used for comparison. Conversely, drug-exposed girls were smaller and lighter in weight. These results suggest that fetal amphetamine exposure in pregnancy accelerates the onset of puberty in boys while delaying the onset in girls. The findings also suggest that amphetamines may interfere with normal neural development and maturation of the adenohypophysis. The deficient education, language, and physical performances among children exposed prenatally to amphetamines raise concerns that the use of amphetamine exposure during pregnancy may produce a wide spectrum of effects. Despite reported detrimental effects, the number of amphetamine-exposed children fell within normal limits. Furthermore, a large number of women in the study used alcohol (81%) and smoked more than 10 cigarettes per day (80%). These confounding variables illustrate the difficulties in assigning cause-and-effect in a polydrug abuse environment. Thus, research conducted using pregnant animals should help resolve the confounding issues of polydrug exposure, environment, and genetic variation.

EFFECTS OF AMPHETAMINES IN PREGNANCY—ANIMAL DATA

Investigations of the prenatal effects of amphetamines in animals have used three approaches. One approach has been to investigate the effects of prenatal exposure to amphetamines on fertility or the devel-

oping fetus. These studies serve to confirm the structural malformations observed after prenatal use of amphetamines in humans. The second approach has been based on the hypothesis that amphetamine use during pregnancy interferes with normal embryonic development of neural structures involving sympathomimetic neurotransmitters, thereby producing permanent functional alterations in those structures and abnormal behavior in the offspring, such as described in the Swedish schoolchildren. The value of this approach is that these results may elucidate issues of altered behavior and learning disabilities seen in humans with prenatal amphetamine use. The third approach in animal models has been to investigate the effects of some of the designer drugs that are psychoactive derivatives of amphetamines. As new compounds are seized from clandestine laboratories, the effects of these compounds are being investigated for their reproductive toxicity in animals, with the assumption that they could be involved in human exposures during pregnancy. The remainder of this review discusses the teratologic effects of amphetamines in animals and whether similar effects are observed in humans. Topics include the behavioral effects of prenatal exposure to amphetamines and the toxicity of some of the psychoactive amphetamine derivatives or designer drugs.

The prenatal effects of amphetamines administered to pregnant animals were first published in two reports in 1965. Bell and co-workers[5] administered *d*-amphetamine sulfate, 3.0 mg/kg intraperitoneally, to pregnant rats on gestational days 6 to 9 or 12 to 15. At the time, it was hypothesized that prenatal stress would result in fetal stress, producing increased "emotionality" and ulcers in the offspring. Although the investigators failed to demonstrate the expected increase in stomach and duodenal ulcers, they did find a reduction in motor activity in 45-day-old offspring.[5] Nora and co-workers[50] demonstrated that administration of 50 mg/kg of *d*-amphetamine intraperitoneally to pregnant A/J mice on gestational day 8 produced increased resorptions and increased malformations in fetuses examined 2 days prior to term. These malformations consisted of cardiac malformations (ventricular septal defect, atrial septal defect, coarctation of the aorta and right aortic arch), cleft lip, eye abnormalities, and skeletal malformations.[50] These first two reports of prenatal exposure to amphetamines demonstrated structural malformations and behavior alterations in offspring, and the results have been the continued focus of ongoing investigations into the prenatal effects of amphetamine exposures in pregnant animals.

The ability of prenatal methamphetamine exposure to produce clefting and optic defects was demonstrated in pregnant CF1 mice and New Zealand White rabbits by Kasirsky and Tansy.[29] Mice were administered 5.0 or 10.0 mg/kg of methamphetamine intravenously via tail vein for 3, 4, or 7 days during days 9 to 15 of gestation, whereas rabbits were administered 1.5 mg/kg intravenously via ear vein for 4, 6, or 18 days during 12 to 30 days of gestation. Another group of male rabbits were treated daily for 3 months with 1.5, 3.0, or 5.0 mg/kg prior to mating. Mice were sacrificed on day 19; rabbits were sacrificed on day 30. In the

mice, there was a dose-dependent and period-of-exposure increase in fetal anomalies, which consisted of exencephaly, eye defects, malformed ribs and vertebrae, and cleft palate. There were also a dose and period-of-treatment increase in whole litter resorptions; increases in the number of resorptions; and decreases in litter size, fetal weight, and maternal weight. The decreased maternal weight was not surprising considering the anorexic effect of methamphetamine. Thus, alterations in maternal weight and, correspondingly, in fetal weight could be accounted for by maternal nutritional intake. Usually, pair feeding would account for any effect an investigational drug may have on dietary intake. However, this study did not take this issue into consideration. Nevertheless, malformations related to vasoconstrictive effects appeared. Exencephaly, ocular defects, malformed ribs and vertebrae, and herniated small intestine were also observed in rabbits exposed to all doses of methamphetamine. Surprisingly, the male rabbits treated with methamphetamine for 3 months prior to mating sired offspring with a number of kidney defects and gastroschisis or who were stillborn. Thus, the results of the study demonstrated that methamphetamine produced malformations in both mice and rabbits.

Although cardiac abnormalities were not observed by Kasirsky and Tansy,[29] Nora and co-workers confirmed in the mouse model the clinical observation that prenatal amphetamine exposure produces cardiac abnormalities. There are several possible explanations why cardiac anomalies were not observed in the study by Kasirsky and Tansy. One reason may be the different doses that were used—5.0 mg/kg[29] versus 50 mg/kg.[50] Another reason may be related to the form of amphetamine used in the two studies—methamphetamine[29] versus *d*-amphetamine.[50] The genetic strain of mouse used in the two studies also differed—CF1 mice[29] versus other mouse strains.[50] In addition to the study in A/J mice,[50] Nora and co-workers compared results in A/J mice with exposures of *d*-amphetamines in C57BL/6J mice.[49] The two strains exhibited different spontaneous cardiac anomalies at low incidence levels: 1.3% atrial-septal defects for A/J strain versus 1.0% ventricular septal defects for B6 strain. After 50 mg/kg of amphetamine exposure, there was a dramatic increase in the respective cardiac anomalies in the specific mouse strain. Thus, the studies demonstrate that the presence of cardiac anomalies and the type of cardiac anomaly are related to the genotype of the mouse strain used. The findings suggest that genetic composition in humans and cardiac defects after prenatal amphetamine exposure could be related.

Cardiac anomalies are not unique to mouse and rabbit models; several prenatal amphetamine exposures have been conducted in chick embryos. In this paradigm, agents of interest are topically applied to the embryo, thereby eliminating the maternal contribution to the prenatal effects of amphetamine. Kolesari and Kaplan[30] exposed 2-day-old chick embryos to 0.5 mg of *d*-amphetamine or 1.0 mg of methamphetamine and examined the embryos 24 hours later. The presence of caudal hematomas; decreased crown-rump length; and a decreased cross-sectional area of the notochord, neural tube, and dorsal aorta are evidence that

early developmental exposure to amphetamines produces rapid onset of hematomas and growth reduction deficits. These deficits are most likely related to vasoconstriction of the embryonic vessels, hypertension, and reduced nutient uptake from the yolk sac. Because the same results were observed when the concentration of *d*-amphetamine was one-half that of methamphetamine, *d*-amphetamine was more teratogenic than methamphetamine in this early embryonic exposure series. This teratogenic characteristic based on dose may account for differences in the mouse data obtained by Kasirsky and Tansy[29] versus Nora and co-workers.[50] Cameron and co-workers[12] exposed 4-day-old chick eggs to 0.1, 0.25, 0.5, 0.75, or 1.0 mg of *d*-amphetamine and examined the embryos 15 days later. Beginning with the 0.25 mg dose, there was a dose-dependent decrease in embryo survival with significant cardiac malformations consisting of persistent left fourth aortic arch and ventricular septal defects. The results indicated that amphetamine not only induced cardiac malformations in this model system but that the malformations were similar to the defects produced when amphetamines were given to pregnant rodents. Moreover, the application of a catecholamine synthesis inhibitor (alpha methyl-p-tyrosine), a beta-1–blocker (metoprolol), and an alpha-blocker (phentolamine) all reduced cardiac malformations induced by *d*-amphetamine. These results with blocking agents suggest a mechanism for the cardiac teratogenesis; however, a common mechanism provided by all three blocking agents was not provided by the researchers. In addition, survival as determined in this study was not improved after the application of blocking agents, suggesting other lethal noncardiac effects of amphetamines, and that survival was not dependent on removal of the cardiac malformations.

Functional cardiac changes have been reported after prenatal amphetamine exposure. Fein and co-workers[19] exposed albino mice to 50 or 100 mg/kg of *d*-amphetamine between gestational days 9 and 11 and examined the fetuses along with unexposed control fetuses on gestational days 15 or 19. The fetuses were evaluated for malformations and altered electrocardiographic (ECG) patterns. In addition, samples of myocardium were removed for histologic examination. There was a dose-dependent increase in the number of resorption sites and malformations and a dose-dependent decrease in maternal survival. Malformations included exencephaly, malformed limb, cleft lip, and eye. No malformations were observed in the control group. Nonmalformed fetuses were then subjected to ECG analysis by determining the time length of the Q-T interval in milliseconds. As is true for many other embryologic neuroelectric signals, the Q-T interval decreases considerably with increasing gestational age. For example, between days 11 and 19, the Q-T interval in mice shortens from a range of 600 to 1000 msec on day 11 to a range of 100 to 500 msec by day 19. Thus, prenatal exposure to substances such as amphetamines could interfere with normal development of the Q-T interval in drug-exposed fetuses and result in a prolonged Q-T interval. There was no significant difference in the Q-T interval at 15 days. However, the amphetamine-exposed fetuses

exhibited a longer Q-T interval in comparison with unexposed controls by day 19. These data suggest that prenatal amphetamine interfered with functional development of cardiac rhythm. Histologic findings demonstrated that amphetamine exposure produced microscopic alterations indicated by the presence of cardiac muscle cells with larger nuclei and clear cytoplasm that were not present in myocardium from control fetuses.

Other investigators have used isolated rat embryos in an attempt to remove the developing embryo from maternal vasoconstrictive effects, hypoxic effects, and anorexic effects and, as a result, have tested directly the effects of amphetamine on the fetus. Yamamoto and co-workers[74] cultured 10.5-day-old gestational age rat embryos in the presence of 0.1, 0.2, 0.4, 0.6, or 0.8 mM of *d*-methamphetamine for 24 hours and then noted the appearance of malformations and growth impairment. Dose-dependent decreases in yolk sac diameter, crown-rump length, the number of somites, and protein content indicated that methamphetamines had direct effects independent of vasoconstriction that occurred over a relatively short period of time. The disadvantage of this isolated embryo model system is that the route of fetal exposure is analogous to exposure through the amniotic fluid and fetal skin.

Because of the appetite-suppressive effect of amphetamine, reducing maternal nutritional intake, it is reasonable to expect reduced maternal and fetal weights and reduced growth in fetuses exposed prenatally. Indeed, none of the rodent studies described previously used a pair-feeding paradigm that would control for maternal nutritional effects of the drug. Acuff-Smith and co-workers[1] used such a pair-fed control as well as an ad libitum fed group when they examined the offspring of pregnant rats exposed to methamphetamine (5, 10, 15, 20 or mg/kg) during two embryologic periods: (1) early embryologic days 7 to 12 and (2) late embryologic days 13 to 18. In both of the methamphetamine-exposed groups, maternal weight was less than in the ad libitum and the pair-fed groups, demonstrating a reduction in maternal weight as a result of methamphetamine exposure that was related to the drug beyond that of nutritional intake. A similar effect was observed in the offspring. The early exposed group was different from the ad libitum fed group but not from the pair-fed group, which contrasted with data from the late-exposed group, which was lighter in weight in comparison with both the ad libitum and pair-fed control groups. Collectively, the data demonstrate that there are additional drug-related mechanisms producing alterations that are not solely the result of reduced nutritional intake. One of these mechanisms could be the vasoconstrictive effects of methamphetamine on the uteroplacental vasculature, which, in turn, would reduce nutrient delivery to the embryo to a further extent than diet alone. In addition, embryos exposed prenatally to methamphetamine during the late embryonic period seem to be more sensitive than embryos exposed during the early embryologic period. Several ocular deformities are noted, including anophthalmia, microphthalmia, and folded retina. Folded retina was also found in the pair-fed group; how-

ever, other ocular malformations were not observed. Thus, with the use of a pair-fed control group, the study by Acuff-Smith and colleagues[7] demonstrated effects of amphetamine beyond that of suppressed maternal nutritional intake.

Studies of the ability of amphetamines to affect behaviors in adults have demonstrated several neurologic and behavioral alterations, including long-term changes in dopamine (DA), serotonin (5-HT), DA and 5-HT metabolites, and DA and 5-HT transporters; a reduced number of reuptake sites; and reduced enzymatic activity of the biosynthetic machinery for these neurotransmitters resulting in nerve terminal degeneration.[63] Altered behavior associated with amphetamine exposure has been demonstrated to differ between adult male and female rats. Female rats exhibit greater locomotor activity and rotational behavior in response to amphetamines in comparison with male rats.[2, 6, 39, 54, 60, 62] This characteristic is explained primarily by the fact that amphetamines are metabolized more rapidly by male rats, resulting in lower brain levels of amphetamines in the adult males.[40] The increased sensitivity of female rats is also directly related to the period of the estrous cycle[4] and is reduced dramatically by ovariectomy.[3, 55] Because brain levels of amphetamines are not altered by estrus,[4] the findings in female rats suggest that steroidal hormones are responsible for such sensitivity. When ovariectomized rats are treated with estradiol for 4 days, they exhibit increased amphetamine-induced rotational behavior, emphasizing the influence of gonadal steroid hormones in this increased sensitivity.[3] The results in female rats suggesting that estradiol and progesterone increase the sensitivity to amphetamines raise the question of such an influence in humans. The increased sensitivity in cycling or pregnant women could potentially produce desired euphoric effects at lower doses. Progesterone and pregnancy are known to increase the sensitivity of female sheep to intravenous cocaine; cocaine causes increased hypertensive responses in progesterone-treated nonpregnant and in pregnant sheep when compared with untreated, ovariectomized nonpregnant sheep.[53, 73] The influence of pregnancy and the related modulation of gonadal steroid hormones seem to have dramatic effects on the behavioral and physiologic responses to amphetamines and cocaine.

In view of the effects in adults, it is not at all surprising that prenatal exposure to amphetamines would interfere with neurologic development and produce permanent behavioral alterations in offspring. Numerous studies demonstrate that prenatal amphetamine exposure results in altered motor activity in offspring. Depending on a number of factors, prenatal exposure to amphetamines can increase or decrease motor activity, produce better performance on active avoidance tasks, worse performance on passive avoidance, worse performance on a Lashley III maze, augmented acoustic startle responsiveness, worse performance on multiple T maze (Cincinnati water maze), and longer latency to find a hidden platform (Morris maze).* Inconsistencies in motor activity data

*References 5, 14, 26, 36, 37, 59, 68, 69, and 71.

are probably related to differences in drug dose, duration of drug exposure, gestational time of exposure, and the age at which the offspring are tested.[41] Data demonstrating poor performance by animals on learning and memory tasks after prenatal or postnatal exposure to amphetamines could parallel the learning deficits reported in the Swedish study of schoolchildren. Despite confounding variables of the human data, prenatal amphetamine (or methamphetamine) exposure seems to increase the risk of learning disabilities in humans.

Other learning tasks affected by prenatal amphetamine exposure seem to be related to age or to the length of offspring testing. This characteristic was demonstrated in a study by Nasello and Ramierez[46] in which the offspring of amphetamine-exposed pregnant rats made more errors in a Lashley III maze in comparison with unexposed controls during the first 4 days of testing. However, after day 4, there was no difference in the numbers of errors committed by the amphetamine-exposed offspring or the unexposed controls.[46] Postnatal brain development in rodents until 10 days is comparable with human brain development during the third trimester in utero.[56] Thus, a number of studies have involved exposures of early postnatal rats and later behavioral testing. Vorhees and co-workers[68] demonstrated that postnatal amphetamine exposure resulted in an augmented acoustic startle response, which also occurs with other agents producing selective DA and 5-HT alterations. This alteration in the startle response seems to be permanent, because long-term testing demonstrates persistence of the augmented response with no alteration of inhibitory pathways responsible for the neurologic changes.[70] Evidence that postnatal amphetamine exposure produces alterations in memory tasks suggests a sensitivity to amphetamine exposure in the third trimester in humans. However, Acuff-Smith and co-workers[1] demonstrated that early embryonic exposure to high-dose methamphetamine produced impaired memory (passive avoidance, Morris maze, Cincinnati maze). Collectively, the data imply that prenatal and postnatal exposure of rodents to amphetamines produces behavioral changes consistent with impaired learning and memory functions.

A limitation of rodent studies is that they cannot provide information about placental transfer of amphetamines, pharmacokinetics in mother and fetus, or maternal and fetal physiologic responses. Such clinically useful information is provided by research in larger animals, such as the chronically catheterized pregnant sheep. Burchfield and co-workers[10] examined the effects of *d*-methamphetamine when administered to chronically catheterized pregnant ewes and their fetuses to determine the fetal and maternal physiologic responses and pharmacokinetics of transfer. In these studies, dosages of 0.6 and 1.2 mg/kg of methamphetamine infused over a 12.5-minute period or 1.2 mg/kg as a 30-second bolus were used. The results demonstrated that methamphetamines readily and rapidly crossed the placenta into the fetal compartment, equilibrating with maternal serum levels at approximately 20 minutes after administration. Furthermore, fetal elimination of methamphetamine was slower than maternal elimination, indicating that the

compound remains in the fetal compartment for a longer period of time when compared with the maternal compartment. The distribution of methamphetamine in fetal tissues indicated that, 2 hours after administration, a six-fold greater amount was found in the fetal brain when compared with the fetal plasma. Maternal hypertension was observed with all administrations of methamphetamine, with a significant elevation above baseline 45 to 120 minutes after administration, indicating a long period of drug action. The method of intravenous administration influenced maternal heart rate, producing tachycardia with the bolus administration and bradycardia with the two infused doses. Although uterine blood flow was not determined in these studies, significant reductions in fetal oxyhemoglobin at the 1.2 mg/kg doses indicate that vasoconstriction of the uterine/placental vasculature occurred to impair fetal oxygen levels. The data demonstrated that amphetamines produced increased vascular resistance to blood flow (vasoconstriction) in the uterine/placental vasculature. In addition to changes in fetal oxygenation, fetal hypertension and fetal tachycardia occurred.

In many respects, these physiologic responses in the pregnant ewe and fetus are similar to the responses observed with bolus administration of cocaine.[45, 72] Several notable differences are present, however. One is the lack of a delayed fetal tachycardia, which, in the cocaine studies, was attributed to cocaine-induced fetal hypoxemia, as well as a direct effect on the fetal heart. This may indicate that the concentration of cocaine used in the studies produced cardiovascular effects that were greater than those of methamphetamine. Both studies indicated that fetal hypertension occurred, which may predispose the fetus to cerebral hemorrhage observed clinically in amphetamine-exposed infants. Although methamphetamine seems to be metabolized quicker in sheep when compared with humans, amphetamines in the fetus seem to have a longer half-life when compared with their activity in the mother, suggesting that the fetus may experience prolonged exposure to amphetamines.

DESIGNER AMPHETAMINES

Addition of substituents on the benzene ring of the amphetamine molecule produces potent hallucinogenic designer drugs (see Fig. 1). Currently, there is no information available concerning the effects of these clandestine laboratory–produced compounds on the human fetus or pregnancy. Adverse outcomes occurring with these compounds may be routinely classified as the effects of amphetamines or perhaps no drug exposure, depending on the sensitivity and cross-reactivity of the available toxicology screens used to identify these compounds. Some of these drugs have been described previously and seem to act as direct agonists with serotonin receptors and promote the release of serotonin (5-HT). This characteristic is of particular concern, because 5-HT has been demonstrated to be a potent teratogen and is embryotoxic during

development.[32, 44, 64, 75] Kramer and co-workers[31] demonstrated that MDMA (methylenedioxymethamphetamine) released tritium-labeled 5-HT from cortical synaptosomes harvested from day 17 rat embryos. Thus, the designer amphetamine MDMA could affect neural release of serotonin in vivo during development and interfere with normal neurologic development.

Bronson and co-workers[7] examined the effects of MDMA and other MDMA analogues on embryonic motility (fetal movements) using single injections of the compounds into day 14 chick embryos and 1-day-old chicks. Adverse effects observed with these designer amphetamines were decreased brain and body weight in the offspring and decreased motility. One of the compounds, 3,4,methylenedioxyphenyl-2-butamine (BDB), was found to be lethal to 60% of the embryos at the highest dose used in the study. These results are striking because the effects occurred with only a single exposure to BDB. Concern in regards to similar analogues is warranted, because virtually nothing is known about these compounds, which occur as synthesis by-products and are likely sold as MDMA.

Other clandestine-produced amphetamines include 4-oxo derivatives. Buttar and co-workers[11] examined the prenatal and postnatal effects of 4-oxo–substituted amphetamines, including 4-hydroxyamphetamine (4-HA), 4-methoxyamphetamine (4-MEA), 4-ethoxyamphetamine (4EA), 4-propoxyamphetamine (4-PPA), and 4-benzyloxyamphetamine (4-BEA) in pregnant mice. Exposure of pregnant mice to 50 or 100 mg/kg of each of these compounds occurred via gavage from gestational day 6 to 18; the live pups were then monitored to 6 weeks of age. Most of the adverse effects of the 4-oxo amphetamines occurred at the highest dose, with 4-MEA being the most fetotoxic, because no viable offspring were observed with the 100 mg/kg dose. One of the typical sequelae of amphetamine and methamphetamine exposure in pregnancy is prematurity. In contrast, exposure to the 4-oxo–substituted amphetamines was associated with prolonged parturition or even failed parturition, with a rank order assigned by the researchers as 4-MEA>4-ETA>4-PPA>4-BEA>4-HA. The incidence of maternal death was observed at 100 mg/kg with all 4-oxo derivatives except 4-PPA, with most deaths occurring with 4-MEA. Cumulative offspring mortality was measured to 3 weeks of age and was associated with all doses of each compound with the exception of 4-ETA at 50 and 100 mg/kg and 4-HA at 100 mg/kg. Thus, fetal, neonatal, and maternal lethality occur with exposure to these 4-oxo amphetamines. Other adverse outcomes include reductions in fetal and neonatal weights, which are most likely related to vasoconstriction in the uteroplacental vasculature. Despite these fetal and maternal mortalities, there were no gross malformations in any of the fetuses examined. Thus, the study demonstrated that maternal and fetal toxicity are associated with prenatal exposure to 4-oxo–substituted amphetamines, with a variation of toxicity among the compounds examined. 4-MEA seems to be most toxic, whereas 4-HA is the least toxic. In contrast to these findings, St. Omer and co-workers[66] examined the effects of

MDMA on the offspring of pregnant rats that had been gavaged with 2.5 or 10 mg/kg of MDMA on alternate days between gestational days 6 and 18. Despite reductions in maternal weight gain and dose-dependent decreases of 5-HT in maternal brain areas, MDMA at this exposure profile produced no effect on litter sizes or birth weights or any malformations in the offspring.

SUMMARY

Based on findings in humans and the confirmation of prenatal exposures in animals, amphetamines and methamphetamines increase the risk of an adverse outcome when abused during pregnancy. Clefting, cardiac anomalies, and fetal growth reduction deficits that have been seen in infants exposed to amphetamines during pregnancy have all been reproduced in animal studies involving prenatal exposures to amphetamines. The differential effects of amphetamines between genetic strains of mice and between species demonstrate that pharmacokinetics and the genetic disposition of the mother and developing embryo can have an enormous influence on enhancing or reducing these potential risks. The effects of prenatal exposure to amphetamines in producing altered behavior in humans appear less compelling when one considers other confounding variables of human environment, genetics, and polydrug abuse. In view of the animal data concerning altered behavior and learning tasks in comparison with learning deficits observed in humans, the influence of the confounding variables in humans may serve to increase the sensitivity of the developing embryo/fetus to prenatal exposure to amphetamines. These factors and others may predispose the developing conceptus to the damaging effects of amphetamines by actually lowering the threshold of susceptibility at the sites where damage occurs.

Knowledge of the effects of prenatal exposure of the fetus and the mother to designer amphetamines is lacking. Based on the few studies in which designer drugs have been examined in animal models, more questions are raised than answered. Possible reasons why no malformations or significant fetal effects were found in the study by St. Omer include the genetic strain of rat used, the conservative exposure profile, or the fact that the placenta metabolized MDMA before reaching the embryo. These questions underscore the need for further investigations concerning the prenatal exposure effects of designer compounds and the effects of amphetamine and methamphetamine in general.

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