Fetal Anomalies and Long-Term Effects Associated with Substance Abuse in Pregnancy: A Literature Review

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Abstract

Objectives Substance abuse in pregnancy remains a major public health problem. Fetal teratogenicity results from the effect of these substances during fetal development, particularly when used in combination. This review will focus on and attempt to clarify the existing literature regarding the association of substance abuse on the development of congenital anomalies and the long-term implications in exposed offspring.

Methods Systematic review of available English literature using the PubMed database of all peer-reviewed articles on the subject.

Results A total of 128 articles were included in this review. Alcohol was the most common substance associated with fetal anomalies, particularly facial dysmorphisms and alterations in the central nervous system development. Adverse maternal environments associated with risky behaviors and lack of adequate prenatal care precludes the timely detection of fetal anomalies, confounding most studies linking causality. In addition, although methodological differences and limited availability of well-designed trials exist, substance abuse in pregnancy has been associated with adverse long-term outcomes in infant growth, behavior, cognition, language and achievement.

Conclusion The literature summarized in this review suggests that drug exposure during pregnancy may increase the risk of congenital anomalies and long-term adverse effects in exposed children and adolescents. These conclusions must be tempered by the many confounders associated with drug use. A multidisciplinary approach is paramount for appropriate counseling regarding the known immediate and long-term risks of substance abuse in pregnancy.

Keywords
- marijuana
- cocaine
- methadone
- opioids
- amphetamines
- pregnancy

According to the 2012 National Survey on Drug Use and Health it is estimated that 23.9 million Americans aged 12 or older have used illicit drugs.[1] These include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants or prescription-type psychotherapeutics used non-medically. Among pregnant women aged 15 to 44 years, 5.9% were current illicit drug users[1]; therefore, a relatively large proportion of reproductive age women and fetuses are exposed to drugs making this a concerning problem to public health.

The maternal, fetal, and long-term infant risks, result from the pharmacological effects of these agents (►**Table 1**),

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Table 1 Main characteristics and major fetal effects of drugs during pregnancy

	Rate in pregnancy (%)	Crosses placenta	Mechanism	Pathognomonic defect	Associated major anomalies
Cocaine	6.9	Yes	Inhibition of cathecolamine reuptake	No	Limb reduction syndrome
Marijuana	9–27	Yes	Increase in carboxyhemoglobin	No	None
Opioids	0.1–2.6	Yes	Binding to opioid receptors result in inhibition of neurotransmitter release[a]	No	Congenital heart defects
Amphetamines	0.7–5.2	Yes	Massive release of CNS neurotransmitters	No	Hypoplastic fetal putamen, hippocampus, and globus pallidus
Alcohol	10.8	Yes	Induction of shallow placentation due to apoptosis of extravillious trophoblast reduce placental perfusion resulting in hypoxemia affecting migration of neural crest cells and inducing apoptosis in neural progenitor cells	FAS[b]	Hydrocephaly Optic nerve hypoplasia Micrognathia Short nose Conotruncal heart abnormalities
Tobacco	17.6	Yes	Hypoxia, vasoconstriction, dysregulation of cytotrophoblastic expression and differentiation	No[c]	Cardiovascular/heart defects, limb reduction defects, missing/extra digits, clubfoot, craniosynostosis, anal atresia, undescended testes, growth restriction

Abbreviations: CNS, central nervous system; FNS, fetal alcohol syndrome.
[a]Limited data exists.
[b]FAS (flat midface, short palpebral fissures, short nasal bridge with short nose, long smooth or flat philtrum with narrow vermilion of upper lip, microcephaly).
[c]No consensus on pathognomonic fetal anomalies exists.

along with the consequences of risky maternal behaviors, and associated adverse social environment (e.g., poverty, unemployment, and limited prenatal care). The pharmacological effect on the fetus depends on the agent(s) used, dosage, length, and gestational age at exposure. Discriminating the pharmacological effects from multiple social and other confounders is difficult and precludes definitive conclusions regarding the effects of those agents on fetal development and growth. In addition, prenatal drug exposure can be difficult to assess because of the social implications and providers attitude toward such behaviors during pregnancy.[2]

This review will focus on and attempt to clarify the existing literature regarding the effects of drugs on the development of congenital anomalies and the long-term implications on exposed offspring.

Cocaine

In 2012 there were approximately 639,000 cocaine users aged 12 or older.[1] It has however been reported that the rate of neonates exposed to cocaine has declined from 2000 to 2008 from 15 to 6.9%.[3] Cocaine is a potent stimulant that has effects in the central nervous system (CNS) and in peripheral tissues. It has a small molecular weight and readily crosses the placenta thus directly affecting the fetus.[4] Cocaine's effects are due to the inhibition of the reuptake of catecholamines (serotonin, norepinephrine, and dopamine), resulting in a prolonged activity of these amines. Pregnancy consequences of cocaine use include: (1) increased myometrial contractions and uterine tone; and (2) generalized vasoconstriction and hypertension. Collectively, the reduced placental perfusion that results can lead to multiple adverse outcomes.[5]

Cocaine and Congenital Anomalies

There are several reports suggesting that cocaine exposure during pregnancy may lead to congenital anomalies in the fetus. However, the risk of major structural malformations attributable to in utero cocaine exposure is still undetermined and there is no known pathognomonic defect. In the past a fetal cocaine syndrome was proposed but solid evidence is lacking. Limb reduction defects have been described in the case reports.[6,7] These findings, along with animal experiments led to the hypothesis that cocaine may have vascular disruptive effects along with vasoconstriction and hypoxia.[8] In a retrospective cohort study, 50 pregnant women who admitted using cocaine during pregnancy were compared with a group of patients with polydrug use and drug-free women.[9] The population studied had a similar rate of tobacco smoking during pregnancy and had similar social characteristics. The rate of congenital malformations in the cocaine group was 10%, whereas in the group without drug exposure was 2%.[9] There was no statistical difference between women exposed to cocaine only versus multidrug users. In the cocaine group, two congenital heart diseases (CHDs), one exencephaly, one interparietal encephalocele, and one parietal bone defect without tissue herniation were reported.[9]

Lutiger et al in 1991 reported in a meta-analysis that genitourinary tract malformations were associated with cocaine exposure during pregnancy, irrespective of the control group comparison (no drug use or poly drugs use).[10] Subsequently, the same group in an updated meta-analysis, reported that major malformations had a relative risk (RR) of 1.7 (95% confidence interval [CI] 1.1–2.6) of women exposed to cocaine in comparison to those without drug exposure.[11] However, there was no significance when the risk of major malformations was analyzed in women exposed to cocaine alone as compared with women exposed to cocaine plus other drugs. The authors suggested that the various confounders, also occurring in polydrug/no cocaine users, are responsible for this effect.[11] Others have reported an increased odds ratio (OR) of having a child with cleft palate among women who used cocaine in the periconceptional period (adjusted OR 2.5; 95% CI 1.1–5.4).[12] Moreover, higher OR for cleft palate when cocaine was used during the third trimester has also been reported.[12] In a retrospective study, infants of cocaine user mothers had a higher rate of congenital cardiovascular malformations than those with a negative drug screen.[13]

Singer et al reported the results of a prospective cohort study in which the relationship between prenatal cocaine exposures resulted in increased rates of developmental delay when compared with unexposed infants (13.7 vs. 7.1%, respectively).[14] These findings are likely the result of the direct effect of cocaine on cortical neurodevelopment, leading to morphologic abnormalities in several brain structures, including the frontal cingulate cortex.[15]

Overall, cocaine use has been linked to cause certain anomalies (mainly in case reports). Till date, no characteristic pattern of malformation has been described and the potential role of confounders remains a problem.

Long-Term Effects Related to Cocaine

The available literature on the effect of cocaine on infant growth is nonconclusive. Hurt et al reported in a prospective study that cocaine-exposed children showed significantly lower mean weights and smaller head circumferences than controls over a 30-month follow-up period ($p < 0.01$).[16] Covington et al prospectively followed 540 infants prenatally exposed to cocaine. After controlling for confounders, children at age 7 were up to 1 in. shorter and twice as likely to fall below the 10th percentile in height when compared with controls. These differences were further increased with advancing maternal age.[17] However, not all studies have found a specific association between cocaine and growth. Jacobson et al[18] and Miller et al[19] report that after controlling for other substances, there were no weight or length differences specifically related to prenatal cocaine use. Richardson et al found no effect of prenatal cocaine exposure on height, weight, and head circumference at the age of 6 years.[20]

Behavioral problems in preschool-aged[21] and elementary school-aged children[22,23] have not been related to prenatal cocaine exposure except when in combination with other maternal risk factors.[24–26] Nevertheless, several studies have

revealed alterations in several aspects of executive functioning, including visual-motor ability,[27] attention,[28–30] and working memory.[31] Subtle language delays have been associated with prenatal cocaine exposure and Morrow et al found 2.8 times the risk of learning disabilities between children exposed to cocaine antenatally compared with their nonexposed peers.

In summary, the literature available evaluating long-term effects on growth and neurodevelopment in children exposed to cocaine in utero is contradictory and likely subject to confounding bias as a result of the adverse social environment in which these children live.

Marijuana/Cannabis

It is difficult to estimate the actual rate of marijuana use during pregnancy, as there are limited prospective studies addressing this issue. Most of the available information is based on voluntary patient reporting or random drug screening. However, marijuana is one of the most commonly used drugs in the United States during pregnancy,[32] with reports ranging from 9 to 27% of the pregnant patients.[33]

Delta-9-tetrahydrocannabinol is the active ingredient in marijuana and readily crosses the placenta. The exact mechanism responsible for the pharmacodynamics of marijuana is unknown. Marijuana produces higher blood carboxyhemoglobin than that produced by cigarette smoking. High carboxyhemoglobin may affect fetal oxygenation and ultimately fetal growth and development. In addition, marijuana (and its active agent delta-9-tetrahydrocannabinol) is fat soluble and may take up to several weeks to be excreted, with a tissue half-life of approximately 6 days[34]; thus prolonging exposure to the fetus. Moreover, delta-9-tetrahydrocannabinol modulates genes that encode for cell growth, morphology, ion exchange pathways, and apoptosis during placental development.[35]

Marijuana and Congenital Anomalies

Cannabis has not been definitively linked to teratogenicity in humans, though some studies have found such an association. In a large retrospective study at the John Hopkins Hospital that included 8,350 deliveries, there was no increase rate of congenital anomalies between the marijuana use group versus controls (5.5 vs. 4.5%, respectively).[36] In a prospective study that included 7,301 single births, 309 neonates (4.23%) exhibited one or more congenital anomalies. However, multiple logistic regression analysis failed to reveal a significant association on the use of alcohol, tobacco or cannabis, and congenital anomalies in this population.[37] In a comprehensive study that explored 20 birth defect categories in 15,208 infants, there was no increased risk of congenital anomalies in the infants whose mothers reported using cannabis in the periconceptional period (1 month before conception through 3rd month of pregnancy).[12] Others have reported that the risk of neural tube defects is not increased by the use of marijuana or polydrug use.[38] However, in one study it was reported that there is a fivefold increase of minor physical anomalies compatible with fetal alcohol syndrome in neonates born from mothers who used marijuana during pregnancy (however, some of these women had alcohol intake during pregnancy).[39] In a case–control study from the National Center on Birth Defects and Developmental Disabilities it was determined that there is a twofold increase in the risk of an isolated simple ventricular septal defect in the newborns of mothers who reported using cannabinoids during pregnancy.[40] Others have reported an increased risk of gastroschisis in the offspring of marijuana users after multivariate analysis controlling for maternal demographics, social aspects, and different drug exposures.[41]

In conclusion, the situation regarding an increased risk of birth defects related to prenatal marijuana exposure is unresolved, but most of the literature suggests either lack of teratogenicity or very modest effect.

Long-Term Effects Related to Marijuana

Cannabinoids have not been definitely associated with specific adverse long-term outcomes during childhood and adolescence. Inattention and impulsivity at 10 years have been linked with antenatal marijuana exposure.[42] Furthermore, cannabinoid use in pregnancy has not been associated with lower IQ scores, but it has been related to deficits in problem-solving skills that require sustained attention and visual memory, analysis, and integration.[43–47] In addition, prenatal marijuana exposure has been associated with increased errors of omission in 6-year-old children[47] and academic underachievement, particularly in the spelling and reading areas.[48] Finally, antenatal cannabinoid use has been associated with increased risk for adolescent marijuana and cigarette use in exposed offspring.[49]

Although there are reports linking subtle neurodevelopmental effects associated with antenatal marijuana use, long-term studies reveal effects on behavior, cognition, and achievement, but not on language or growth.

Opioids

Opioids, also referred to as narcotics, are synthetically derived analgesic compounds that have morphine-like pharmacodynamic activity. Heroin is derived from morphine, and produces pharmacologic effects identical to those of the parent drug but more powerful, and because it is a lipophilic drug crosses the blood–brain barrier and placenta rapidly. In contrast, methadone is a long acting, synthetic opioid with similar effects as morphine, but it is used mainly to treat heroin addiction and to manage pain. Similarly, buprenorphine is an opioid analgesic with greater potency than morphine and with agonist–antagonist properties that has been used as an alternative to methadone for opioid dependence. These groups of medications including prescription narcotics (i.e., codeine, hydrocodone, oxycodone, etc.) have increased its prevalence exponentially among pregnant women in comparison from previous years.[3,50] Opioid abuse in pregnancy includes the use of heroin and the abuse of prescription opioid analgesics. It has been reported that 0.1% of pregnant women have used heroin in the past 30 days. In this study, the rate of use varies by setting and mode of assessment. The urine screening of pregnant women in an urban teaching hospital resulted in a detection rate for

opioids of 2.6%.[51] Approximately 2 to 2.5% of pregnant women will admit using opioids during pregnancy as an analgesic.[52] However, the use of heroin and the therapies available for its treatment (methadone, buprenorphine) are a global problem and many of the affected patients are women in childbearing age; hence the importance of knowledge regarding the possible adverse effects in the development of anomalies in the fetus.

Opioids and Congenital Anomalies

In the past, opioids have not been considered teratogenic, at least in terms of gross congenital abnormalities. In fact, several studies did not find a higher incidence of congenital anomalies in mothers exposed to codeine, methadone, or heroin. Similar results have been reported in animal studies at doses of 40 mg/kg.[53]

The Maternal Opioid Treatment: Human Experimental Research [MOTHER] trial, which was a multisite, double-blind, double-dummy, flexible-dosing, randomized, controlled study that compared the use buprenorphine and methadone to evaluate the treatment of opioid-dependent pregnant patients had a sample size of 131 patients.[54] In this study, the authors did not report the rate of fetal anomalies.[54] However, the neonates exposed to methadone had a lower mean birth weight than those neonates exposed to buprenorphine, and in addition, the head circumference and birth length were statistically smaller in the methadone group when compared with the buprenorphine group.[54] Of note, the gestational age when therapy was started was 18.7 weeks in both the groups and 95% or more were cigarette smokers at the time of enrollment. Interestingly, neonates exposed to buprenorphine had less risk of opiate withdrawal as noted by a reduced need and duration of treatment with morphine ($p < 0.009$ and < 0.003, respectively), as well as reduced hospital stay ($p < 0.009$).[54]

Other studies have reported positive associations with congenital anomalies. For example, in a large retrospective cohort study that included more than 61,000 births and 618 neonates exposed to methadone in Ireland, an association between methadone exposure and major congenital anomalies was reported (OR, 1.94; 95% CI 1.10–3.43). The incidence of Pierre Robin sequence was also increased in this cohort (1:155 vs. 1:7,552 in nonexposed neonates) but the authors stated that this was not sufficient to link methadone causally to Pierre Robin sequence.[55] In a descriptive analysis in Switzerland of newborns exposed to methadone during pregnancy (during a 6-year period), the authors reported a high rate of congenital malformations.[56] In this series 15% (12/78) were reported to have a congenital anomaly that included: four cases of cardiac lesions (two with tetralogy of Fallot, one with valvular pulmonary stenosis, and one case with hypertrophy obstructive cardiomyopathy), two cases of cryptorchidism and other anomalies affecting the lower extremities and optic nerve.[56] Of note, only three of these cases with anomalies were reported to only use methadone during pregnancy; the rest were exposed to a combination of drugs that included cocaine or heroin in addition to methadone. Therefore, the interpretation of these results regarding the high incidence without a dominant pattern of anomalies should be taken with caution. In a small report, two opioid dependent women, who were maintained continuously on buprenorphine at the time of conception and during the remaining of pregnancy delivered healthy newborns without major congenital anomalies and appropriate birth weight (one infant had a single umbilical artery without chromosomal abnormalities).[57] A recent report of the Norway national registry of pregnant women with opioid maintenance treatment (methadone or buprenorphine) included 90 neonates exposed to methadone and 49 neonates exposed to buprenorphine.[58] Of these, only two neonates (in the buprenorphine group) were reported to be born with a congenital anomaly; one child with spina bifida and one child with gastroschisis.[58] Unfortunately, there is no mention of whether these fetuses were exposed to additional drugs; but nonetheless, this finding does not represent causality. Moreover, many of the large series, prospective studies, and randomized trials that included methadone and/or buprenorphine do not report congenital anomalies.

In a case–control study that it was intended to estimate the risk of CHD among users of Bendectin (Wm. S. Merrell Company, Cincinnati, OH) (pyridoxine/doxylamine), an antiemetic medication, the authors reported that use of codeine during the first trimester of gestation was associated with CHD.[59] Recall bias may be a limitation of this study as the mean interval period to interview the mother was 14 months after delivery; the authors tried to control for this bias by chart reviewing, but nonetheless this is still a major limitation of the study.[59] These results, prompted a letter to the editor reporting similar findings based on a new analysis of a previous study in which codeine was associated with CHD (OR 4.4; 95% CI 1.3–8.9).[60] Rothman et al intended to determine the risk of CHD in women exposed to exogenous hormones and other drugs during pregnancy. This study included five cases of women exposed to codeine and reported a small positive association with CHD.[61] However, all of these studies had few cases and considered CHD of any type, as a single entity and did not analyze individual heart defects. More recently, a large multisite population-based case–control study in the United States, reported an association between early pregnancy, maternal opioid treatment and certain birth defects, including certain categories of CHD-like conoventricular septal defects (OR 2.7; 95% CI 1.1– 6.3), atrioventricular septal defects (OR 2.0; 95% CI 1.2–3.6), and hypoplastic left heart syndrome (OR 2.4; 95% CI 1.4–4.1).[52] Moreover, it was reported that the risk for spina bifida (OR 2.0; 95% CI 1.3–3.2) and gastroschisis (OR 1.8; 95% CI 1.1–2.9) in infants exposed in utero to opioids during the first trimester of the pregnancy was increased.[52] Of note, codeine and/or hydrocodone accounted for the majority of the statistically significant findings, and oxycodone was only significantly associated with pulmonary valve stenosis.[52] The authors defined opioids as a group that included multiple drugs, including: codeine, hydrocodone, meperidine, oxycodone, propoxyphene, morphine, tramadol, methadone, hydromorphone, fentanyl, and pentazocine but provided individual risk analysis for each drug and congenital anomaly when feasible.[52] Some limitations of this study include that the exposure

information was obtained through retrospective maternal self-reporting, with the risk of attendant recall bias and/or exposure misclassification. Others have reported no association of opioids (heroin or methadone) use during pregnancy and spina bifida, but several confounders may bias this result.[62]

The association of cleft lip and use of narcotics have been reported, but it is important to stress that in one study it was reported that patients used other street drugs[62] and in a second report the authors did not control for the concomitant use of other drugs.[63] In animal models, opiates have shown to decrease fetal brain growth and cell development.[64]

Altogether, it appears that there might be grounds to reconsider the long held view that opioids are not teratogenic. Perhaps the risk effect is small; but a chronic dependence associated with the increase prescription and abuse of these medications appears to be associated with adverse outcomes in the development of the fetus. Nonetheless, the use of drugs, such as methadone and buprenorphine, for opioid-dependent women during pregnancy outweighs the adverse effects of continued use of illicit drugs because the threats to the fetus and mother are greater.

Long-Term Effects Related to Opioids

Long-term effects have not been well documented in children exposed to opiates in utero.[65] In one study, exposed children have demonstrated to have higher rates of decreased visual acuity, nystagmus, delayed visual maturation, strabismus, refractive errors, and cerebral visual impairment.[66] Similarly, in a large population-based case–control study, the risk of glaucoma and anterior chamber defects in infants antenatally exposed to opiates during the first trimester was higher (OR 2.6, 95% CI 1.0–6.6).[52]

Rosen et al reported associations between hyperactivity and short attention span with antenatal opiate exposure.[67] Memory and perceptual problems in older children have also been described.[68] There is a paucity of data available to draw any conclusions in regards to the effect of antenatal opiate exposure on offspring cognition, executive functioning, or academic achievement.

Amphetamines

According to the National Survey on Drug Use and Health in 2012 the number of users of methamphetamine decreased between 2006 and 2012 from 731,000 (0.3%) to 133,000 (0.05%).[1] This decrease was also observed in young adults. There are limited data on the extent of methamphetamine use in pregnancy. National prevalence estimates vary from 0.7 to 5.2%.[69] The National Survey on Drug Use and Health appears to contrast with a recent study from the Treatment Episode Data Set that reported the number of pregnant women who were admitted for treatment of methamphetamine to federally funded centers in the United States in 2006 that showed an increase in admission from 8% in 1994 to 23.7% in 2006.[2] It is worth mentioning, that the use of this drug is more prevalent in the White and Hispanic population (combined 87.4%) and in pregnant women between 21 and 29 years.[2] In fact, since 2003, methamphetamine has been the most common primary substance for treatment admissions among pregnant women to United States federal-funded centers; however, its use is frequently associated with polysubstance abuse (62.4%).[2]

Methamphetamine is a potent sympathomimetic and stimulant agent that causes a massive release of neurotransmitters in the CNS (i.e., dopamine and norepinephrine), thereby inducing experiences of euphoria, increased alertness, irritability, and aggressiveness. Some of the effects are similar to cocaine and may lead to tachycardia, diaphoresis, and seizure. A derivative of amphetamine (3, 4-methylenedioxymethamphetamine [MDMA] or ecstasy) has both stimulant and hallucinogenic effects.

Amphetamine and Congenital Anomalies

There is limited information in the literature regarding the effects of amphetamines in pregnancy, specifically on the subject of fetal anomalies. However, according to some studies the use of amphetamines during pregnancy appears to not be associated with structural abnormalities in the fetus.[70,71] In contrast, the use of MDMA or "ecstasy" during pregnancy; in a prospective study (127 women exposed to ecstasy with 78 live-born infants) in the United Kingdom, was associated with a risk of congenital anomalies of 15.4% (95% CI 8.2–25.4). Of the 78 live-born infants, 12 had congenital anomalies. There were two infants with cardiovascular anomalies (ventricular septal defect and atrioventricular septal defect) and three with musculoskeletal anomalies (talipes).[72] The authors calculated that the rate of CHD and talipes was above the expected rate of the general population (26 per 1,000 live births and 38 per 1,000, respectively). Similar to other studies that evaluate drug exposure during pregnancy, close to 50% of the neonates exposed to ecstasy were also exposed to an additional drug (i.e., alcohol).[72] More recently, in a prospective study that included 28 newborns exposed to MDMA, Fischer et al[73] did not report cases of congenital anomalies other than one child affected with Townes–Brocks syndrome (a rare genetic autosomal dominant syndrome that should not be related to MDMA exposure) but did report that the children had poorer motor and mental development and milestone delays at 4 and 12 months of age.[73,74]

Others have reported increased cases compared with controls of infants with cleft lip whose mothers used amphetamine during the first trimester of pregnancy or in association with other drugs.[62,75] In a matched case–control study that included 144 infants with gastroschisis, in 10 cases the mothers reported using one or more "recreational drug" including ecstasy ($n = 7$), amphetamines ($n = 5$), and cocaine ($n = 2$).[76] The authors reported that after conditional logistic regression analysis, mothers who use of "recreational drugs" (vasoconstrictive) during the first trimester was associated with over a threefold risk of gastroschisis (OR = 3.3, 95% CI 1.0, 10.5).[76] However, nonsignificant results and lower ORs were obtained after performing the analysis with patients in whom drug hair analysis was available. Interestingly, fetuses exposed to methamphetamine (for at least two-thirds of the pregnancy) tended to have smaller brain structures, such as putamen, hippocampus, and globus pallidus as

compared with nonexposed children measured by magnetic resonance imaging.[77] In addition, these findings were associated with neurocognitive deficits and the authors suggested that these findings may represent evidence of methamphetamine prenatal dopaminergic toxicity.[77]

Overall, prenatal amphetamine exposure does not seem associated with any consistent increase or characteristic pattern in congenital anomalies; and many of the reports are confounded by the use of additional drugs, small sample size, and recall bias.

Long-Term Effects Related to Amphetamines

Literature on long-term effects in children exposed to amphetamines in utero is inconclusive. Eriksson et al prospectively followed 65 exposed children from birth to 8 years of age. Poor growth, weight, and head circumference were reported, although potential for confounding bias remains a concern.[78] Similarly, at 14 to 15 years of age, the children in their cohort scored significantly lower on math tests than did their nonexposed classmates.[79]

Alcohol

Alcohol is an anxiolytic analgesic that can have depressant effects on the CNS. Ethanol and its metabolite acetaldehyde are mainly responsible for the biological effects. It is estimated that 10.8% of the women reported use of alcohol during pregnancy, 3.7% reported binge drinking, and 1.0% reported heavy drinking during pregnancy.

The teratogenic and adverse effects of alcohol in fetal growth during pregnancy have been well documented throughout the years.[80] Teratogenicity is thought to occur early in pregnancy when induction of shallow placentation due to apoptosis of extravillious trophoblast reduces placental perfusion. This results in hypoxemia affecting the migration of neural crest cells and inducing apoptosis in neural progenitor cells.[81] It is clear that chronic heavy alcohol consumption has a negative effect of birth weight and may lead to fetal alcohol syndrome. However; the controversy persists related to the amount of alcohol consumed during pregnancy that is considered to be potentially harmful to the offspring and leads to teratogenic effects.

Alcohol and Congenital Anomalies

The amount of alcohol exposure and the susceptibility among pregnant women is broad and therefore the effects on the fetus are broad too. In general, the quantity of alcohol that can lead to fetal damage is estimated to be above one drink (14.8 mL) per day and even less in the case of binge drinking.[82] However, there is no consensus on the safe level of alcohol intake during pregnancy. Fetal alcohol syndrome (FAS) is defined as a combination of growth restriction, characteristic facial features, and cognitive impairment.[83] The classical dysmorphic facial features of FAS include a flat midface with short palpebral fissures, a low nasal bridge with short nose, and long smooth or flat philtrum with a narrow vermillion border of the upper lip.[80,84]

A meta-analysis performed by Polygenis et al[85] in 1998 evaluated the effects of moderate alcohol consumption (24–168 g/wk or at least more than two drinks per week) and the incidence of fetal malformations. This study included 130,810 pregnancy outcomes and reported a RR for fetal malformation of 1.01 (95% CI 0.94–1.08). The authors concluded that moderate alcohol consumption during the first trimester of pregnancy is not associated with increased risk of fetal malformations, but they also cautioned that these results were not intended to justify any drinking during pregnancy.[85] A systematic review by Henderson et al[86] concluded that there was not enough evidence to associate low-to-moderate (less than 84 g/wk and/or an infrequent drinker [< 6 g/wk] alcohol consumption) with birth defects.

The most common congenital abnormalities linked to alcohol are those of the CNS and face. These include microcephaly,[87,88] hydrocephaly,[87] optic nerve hypoplasia,[89] micrognathia,[90] short nose,[80,90] hypoplastic philtrum,[80,90] cleft lip/palate[88,91] have all been reported. Cardiac defects such as conotruncal anomalies have also been reported.[88,92]

Overall, alcohol is a known teratogenic drug, especially in heavy drinker; however, the current evidence regarding low or moderate alcohol consumption during pregnancy appears not to have the same effect.

Long-Term Effects Related to Alcohol

Although poor growth is one of the hallmarks of fetal alcohol syndrome, it is the least sensitive of the diagnostic criteria.[93] Antenatal alcohol exposure has been linked with significant attention problems in the offspring, comparable with those children with attention deficit hyperactivity disorder.[94,95] Furthermore, adaptive behavior problems, including disrupted school experiences, delinquent and criminal behavior, inappropriate sexual behaviors, and substance abuse have all been reported in children exposed to alcohol in utero.[96]

Antenatal alcohol exposure is frequently cited as the most common, preventable cause of nongenetic intellectual disability. It has been associated with lower IQ scores, impaired memory, and executive functioning skills.[97–99] Moreover, children born to heavy drinking mothers have increased rates of language and communication disabilities, as well as school problems, particularly related to reading and math skills.[100–103]

Cigarette Smoking

According to the National Survey on Drug Use and Health in 2012 about one in six pregnant women aged 15 to 44 had smoked cigarettes 1 month before the survey.[1] The rate of current smoking among pregnant women did not change between 2002 and 2003 (18%), and 2010 and 2011 (17.6%), while among women aged 15 to 44 who were not pregnant, the rate declined from 30.7 to 25.4%.[1]

In addition to nicotine and carbon monoxide, there are hundreds of chemicals and additives in each cigarette that can be potentially harmful to the fetus. Carbon monoxide can interfere with oxygen delivery by displacing oxygen from

hemoglobin, and by shifting the oxyhemoglobin dissociation equilibrium to the left. On the other hand, nicotine increases maternal catecholamines and can cause uterine artery vasoconstriction. Moreover, maternal smoking directly dysregulates cytotrophoblast expression and differentiation, a mechanism thought to be responsible for some of the adverse outcomes seen in pregnancy.[104]

Cigarette and Fetal Anomalies

A meta-analysis that evaluated the association between maternal cigarette smoking and oral clefts found an overall RR of 1.34 (95% CI 1.25–1.44).[105] This risk was similar when the analysis was limited to isolated or multiple cleft lips with or without cleft palate. A previous meta-analysis with fewer studies reported similar results.[106] More recently, a comprehensive systematic review and meta-analysis that included studies from 1959 until 2010 examined the associations between maternal smoking and nonchromosomal birth defects.[107] Total 172 articles were included with more than 173,687 cases and 1,1674,332 unaffected controls. There were multiple positive associations between maternal smoking and specific malformations. Of importance is that all the significant OR, except for gastroschisis, were below 1.50.[107] A partial list of birth defects positively associated with maternal cigarette use during pregnancy are: cardiovascular/heart defects, musculoskeletal defects, limb reduction defects, missing/extra digits, clubfoot, craniosynostosis, gastrointestinal defects, anal atresia, hernia, and undescended testes. Of these positive associations some effects appeared modest (digit anomalies, cryptorchidism, heart, and musculoskeletal system) others were more substantial (limb reduction defects, clubfoot, oral clefts, gastroschisis, and abdominal hernias) and as proposed by the authors, they should be taken into consideration at the time of prenatal counseling.[107] Regarding cardiovascular/heart defects, it appears that ventricular septal defect (VSD) and atrial septal defect (ASD) had the strongest association with maternal smoking. Absence of or severe underdevelopment of the hands or feet, radius, tibia, ulna or fibula were the musculoskeletal defects associated with smoking. Osteoblast differentiation is affected by nicotine via inhibiting the proteins that stimulate bone formation.[108] In the analysis of gastroschisis there were 12 studies included in the analysis and all but one showed an increased risk of gastroschisis. No significant difference was found in the frequency of omphalocele. Of interest, maternal smoking during pregnancy was associated with a reduction in the risk for hypospadias, (OR 0.90; 95% CI 0.85–0.95). In addition, there was no evidence of maternal smoking during pregnancy and spina bifida, anencephaly, congenital diaphragmatic hernia, anomalies in the respiratory system, and renal/urinary tract.[107]

Passive smoking has been associated with increased risks of congenital anomalies (OR 1.17; 95% CI 1.03–1.34) and a trend toward reduction of head circumferences (–0.11 cm; 95% CI –0.22 to 0.01 cm).[109] Brain tumors, despite not considered as a congenital anomaly, it was reported to be increased fourfold in children less than 2 years whose mothers smoked during pregnancy.[110]

Smoking during pregnancy has a modest effect on the rate of fetal anomalies, but due to the additional negative effects that can affect the course of the pregnancy (i.e., growth restriction, placental abruption); counseling against smoking should be encouraged at all stages of pregnancy.

Long-Term Effects Related to Cigarette Smoking

Although there is extensive literature documenting the negative effects of tobacco during pregnancy on fetal growth, there is a paucity of reports on the long-term effects on exposed offspring. Fried et al reported a tendency among adolescent offspring born to smoking mothers to be more overweight when compared with controls.[111]

After controlling for confounding factors, prenatal tobacco exposure has been associated with impulsivity, attention problems,[112–114] hyperactivity,[115] and negative[116] or externalizing behaviors in children,[117–119] which appears to continue through the adulthood in the forms of higher rates of delinquency, criminal behavior, and substance abuse.[120–125] In addition, children exposed to nicotine in utero have poor language development and learning disabilities associated with slightly lower IQ levels when compared with controls.[120,126,127] Poor language and reading abilities in late childhood have also been reported.[128]

Conclusion

The literature summarized in this review suggests that drug exposure during pregnancy of some agents may increase the risk of congenital anomalies and long-term adverse effects in exposed children and adolescents. These conclusions must be tempered by the many confounders associated with drug use. Despite this caveat, the preponderance of the evidence confirms a positive effect on anomaly development. In consequence, a comprehensive anatomy ultrasound followed by a late second or third trimester growth assessment may be of value in identifying potential congenital anomalies or impaired fetal growth. While current evidence associating substance abuse with long-term intellectual disability in exposed infants is limited; large prospective studies are urgently needed to further elucidate this association. In the meantime, systematic evaluation for and appropriate counseling regarding the known risks of substance abuse should be a standard feature of prenatal care in all women, regardless of socioeconomic or racial/ethnic status.

Conflict of Interest
The authors have no conflicts of interest to disclose.

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