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TERATOGEN UPDATE

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Teratogen update: Amphetamines

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Abstract

Amphetamines are synthetic noncatecholamine sympathomimetic amines that act as psychostimulants. They have been prescribed for the treatment of attention-deficit/hyperactivity disorder (ADHD), narcolepsy, and additional health conditions. Amphetamines are also drugs of abuse. Some experimental animal studies suggested adverse developmental effects of amphetamines, including structural malformations. These effects were most often observed in experimental animals at higher dose levels than those used for treatment or abuse and at dose levels that produce maternal toxicity. Controlled studies of amphetamine use for the treatment of ADHD and other indications did not suggest that amphetamines are likely to cause structural malformations, although there are three studies associating medication for ADHD or methamphetamine abuse with gastroschisis. We did not locate studies on the neurobehavioral effects of prenatal exposures to therapeutic amphetamine use. Amphetamine abuse was associated with offspring neurobehavioral abnormalities, but lack of adequate adjustment for confounding interferes with interpretation of the associations. Adverse effects of methamphetamine abuse during pregnancy may be due to factors associated with drug abuse rather than methamphetamine itself. The adverse effects observed in methamphetamine abuse studies may not be extrapolatable to amphetamine medication use.

KEYWORDS

amphetamines, birth defects, methamphetamine, neurobehavior, pregnancy

1 | INTRODUCTION

Amphetamines are synthetic noncatecholamine sympathomimetic amines that act as psychostimulants. Amphetamines are prescribed for the treatment of attention-deficit/hyperactivity disorder (ADHD) and narcolepsy and less frequently prescribed for weight loss. While the use of amphetamines as a treatment for weight loss has diminished over time, the number of adults diagnosed with ADHD has increased as has the prescribing of amphetamines to treat ADHD. According to data from the National Birth Defects Prevention Study (U.S.), between the years 1998 and 2011, about 0.5% of women used ADHD medication during pregnancy and the number of such women more than doubled during that time period (Anderson et al., 2018). A study from Denmark found that from 2003 to 2010, pregnancy use of ADHD medication increased from 5 to 533 per 100,000 person-years (Hærvig, Mortensen, Hansen, & Strandberg-Larsen, 2014).

Amphetamines are also drugs of abuse and this abuse can extend into or start in pregnancy. In the U.S., between 2008 and 2009, approximately 0.12% of all hospital deliveries were amphetamine abuse-associated (Admon et al., 2019). Between 2014 and 2015, this value doubled. In the rural western U.S., the prevalence of amphetamine

abuse-associated deliveries in 2014–2015 reached as high as 1%, higher than the prevalence of opioid-associated deliveries in most locations (Admon et al., 2019).

In 2005, the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction produced a monograph on the potential human reproductive and developmental effects of amphetamines (Golub et al., 2005). The monograph included a review of data available through 2003. Concern was expressed over the safety of controlling ADHD symptoms with amphetamines during pregnancy, and the monograph indicated that additional studies were needed (Golub et al., 2005). The purpose of this teratology update is to present the current knowledge of possible pregnancy effects of amphetamines. The potential effects covered include structural malformations, growth effects, and neurological effects in offspring and maternal effects including preeclampsia and premature delivery. Additional experimental animal and epidemiology studies of pregnancy exposures to methamphetamines have been conducted since 2003. More recent data also exist on the health consequences of methamphetamine abuse during pregnancy.

2 | TYPES OF AMPHETAMINES

2.1 | ADHD agents

The group of substances known as amphetamines and currently used as prescription drugs for the treatment of ADHD is comprised of amphetamine, dextroamphetamine (D-amphetamine), lisdexamfetamine, and methamphetamine. Racemic amphetamine is a mixture of dextroamphetamine and levamphetamine (L-amphetamine), with dextroamphetamine having the greater potency of the two. At one time, levamphetamine was used as the active ingredient in an over-the-counter nasal decongestant inhaler marketed as Benzadrine. Methamphetamine, a substituted amphetamine, also exists as two stereoisomers. Some over-the-counter nasal decongestant inhalers, including one marketed as Vicks® VapoInhaler®, have contained levomethamphetamine (referred to on product labeling as L-desoxyephedrine or levomethamphetamine) as a sympathomimetic vasoconstrictor (Mendelson et al., 2008). Methamphetamine is metabolized in the rat liver to amphetamine, 4-hydroxymethamphetamine, norephedrine, hippuric acid, 4-hydroxyamphetamine, and 4-hydroxynorephedrine (Caldwell, Dring, & Williams, 1972). The metabolism of methamphetamine to amphetamine also has been demonstrated in humans (Oyler, Cone, Joseph Jr., Moolchan, & Huestis, 2002). Lisdexamphetamine is a prodrug of dextroamphetamine. Brand names in the U.S. for prescription amphetamines used in the treatment of ADHD, their active ingredient(s), and their U.S. FDA-approved indications as of May 1, 2020 are displayed in Table 1.

For the treatment of ADHD, there are additional agents used that are not amphetamines. These agents include methylphenidate (Ritalin®), atomoxetine (Strattera®), and modafinil (Provigil®). Methylphenidate is a psychostimulant medication comparable in presumed mechanism of action

TABLE 1 Brand names of prescription ADHD medications containing amphetamines[a,b,c]

Name	Chemical(s)	Indication(s)
Adderall®; Adderall XR®	Dextroamphetamine saccharate Amphetamine aspartate Dextroamphetamine sulfate Amphetamine sulfate[d]	ADHD and narcolepsy
Adzenys ER™; Adzenys XR-ODT™	Amphetamine	ADHD
Desoxyn®	Methamphetamine hydrochloride	ADHD and weight loss
Dexedrine® Spansule®	Dextroamphetamine sulfate	ADHD and narcolepsy
Dyanavel® XR	Amphetamine	ADHD
Evekeo®; Evekeo ODT®	Amphetamine sulfate	ADHD and narcolepsy
Mydayis®	Dextroamphetamine saccharate Amphetamine aspartate Dextroamphetamine sulfate Amphetamine sulfate[d]	ADHD
ProCentra®	Dextroamphetamine sulfate	ADHD and narcolepsy
Vyvanse®	Lisdexamfetamine dimesylate	ADHD and binge eating disorder
Zenzedi®	Dextroamphetamine sulfate	ADHD and narcolepsy

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.
[a]Information in this table obtained from the drug labeling for each agent available at DailyMed, https://dailymed.nlm.nih.gov/dailymed/.
[b]All of these agents except for Vyvanse® are available as generics.
[c]All of these agents are for oral administration.
[d]Adderall® and Mydayis® are mixtures of the enantiomers dextroamphetamine and levoamphetamine salts in a 3:1 ratio.

to amphetamine-based agents. Atomoxetine, a selective inhibitor of the presynaptic norepinephrine transporter, is a nonstimulant agent (Wilens, 2006). Modafinil, a racemic sulfoxide derivative, is a centrally active α1-adrenergic agonist that acts as a psychostimulant. The potential effects of non-amphetamine medications in pregnancy are not covered in detail by this review, although methylphenidate and atomoxetine have been studied and compared to amphetamines in clinical research on ADHD treatment during pregnancy (Anderson et al., 2018).

As recreational drugs, amphetamine and methamphetamine have street names including meth, speed, crystal, glass, ice, crank, and yaba. While all amphetamine types are abused as stimulants, methamphetamine is known for the induction of euphoria, has the highest potential for addiction, and is the most often abused. Methamphetamine is more potent than amphetamines in the central nervous system (CNS), and effects last for 6–8 hr (U.S. Drug Enforcement Administration, 2020). Euphoria is enhanced by injecting the agent instead of taking it orally. Smoking and snorting of crystallized methamphetamine are other modes of administration.

The CNS actions of amphetamines are attributed to structural similarity to dopamine and other β-phenylethylamines (Figure 1; see Heal, Smith, Gosden, & Nutt, 2013). According to a systematic review of the literature on CNS actions of amphetamine by Faraone (2018), the primary pharmacologic effect of amphetamine is to increase central dopamine and norepinephrine activity. The trace amine-associated receptor 1 (TAAR1) is a G-coupled receptor expressed in the monoaminergic regions of the brain (Lam et al., 2018). When activated by appropriate ligands including methamphetamine, dopaminergic function is modulated (Miner, Elmore, Baumann, Phillips, & Janowsky, 2017). Amphetamine also has actions at the acetylcholine, serotonin, opioid, and glutamine receptors, and increases blood flow in the brain (Faraone, 2018).

Amphetamines are also vasoconstrictors. It has long been assumed that amphetamines are indirectly acting sympathomimetic amines, with responses being due to the release of norepinephrine from sympathetic neurons (Broadley, 2010). With the discovery of TAAR in blood vessels and evidence that amphetamine binds to these receptors, it has been suggested that the vasoconstrictor effect may be due in part to this additional mechanism (Broadley, Fehler, Ford, & Kidd, 2013).

2.2 | Amphetamine prodrugs

There are at least three medications available today that are prodrugs for amphetamine and/or methamphetamine and thus constitute potential sources of amphetamine exposure during pregnancy and lactation. None of these drugs are marketed for the treatment of ADHD. Fenproporex, a compound with structural similarity to amphetamine and prescribed as an anorectic drug, is 60–80% converted to amphetamine in rats and humans (see review by Paumgartten, Pereira, & de Oliveira, 2016). While data on fenproporex could be considered relevant to the possible developmental effects of amphetamine, we did not locate adequate studies on human pregnancy outcomes after fenproporex exposure. Fenproporex is no longer available in the U.S., although it is available in some other countries.

Benzphetamine hydrochloride, prescribed as an anorectic and once marketed as Didrex, is a prodrug for dextroamphetamine and dextromethamphetamine in rats (Kikura & Nakahara, 1995), monkeys (Banks, Snyder, Fennell, & Negus, 2017), and humans (Cody & Valtier, 1998). In the U.S., benzphetamine hydrochloride is available as a generic drug. We did not locate experimental animal or human pregnancy or lactation studies of this agent. As with other amphetamine prodrugs,

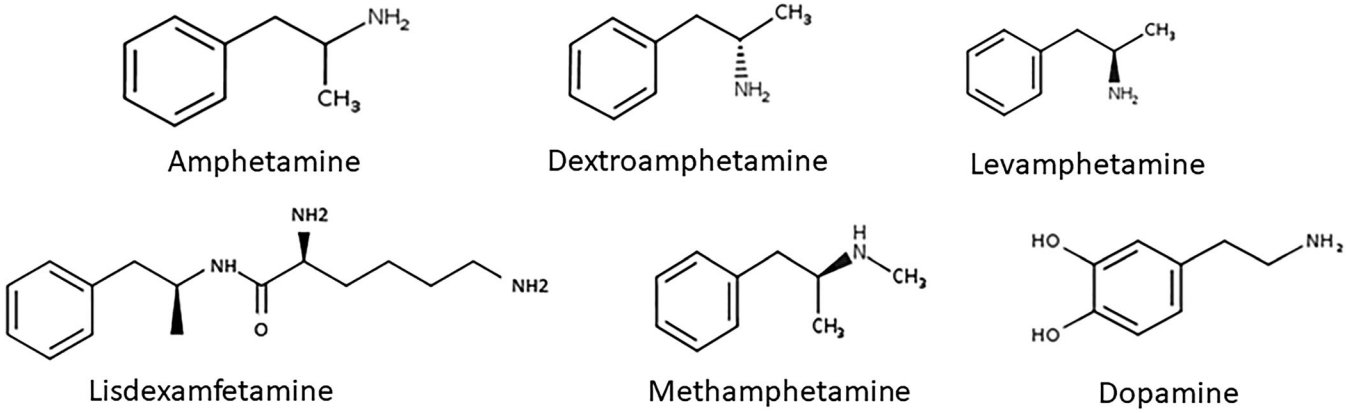

FIGURE 1 Structural comparison of amphetamine group members to dopamine

nonclinical data on reproductive toxicity of the agent were not generated, and reproductive toxicity data on amphetamines were used to address regulatory requirements. Banks et al. (2017) examined the relationship between the timing and plasma concentrations of benzphetamine and metabolites in monkeys for correlation with behavioral effects of the drug. It was concluded that there may have been an additional unidentified metabolite that contributed to behavioral effects. Unidentified metabolites would decrease the predictivity of nonclinical data on dextroamphetamine and dextromethamphetamine.

Clobenzorex, used as an anorectic, is a prodrug of dextroamphetamine. Clobenzorex is no longer available in the U.S. as a prescription drug. It is marketed elsewhere as Asenlix®, Benturex®, Ezbencx®, Itravil®, Obeclox®, and Redicres. This agent has been used by athletes as a performance-enhancing drug. Because of the green color, Asenlix® capsules are referred to as greenies, a name also used to refer to amphetamines in general. The pregnancies of 23 patients with first trimester exposure to clobenzorex resulted in four elective abortions, one medical abortion, one fetal death, and 17 normal births, with no congenital abnormalities observed (Vial, Robert, Carlier, Bertolotti, & Brun, 1992).

2.3 | Other drugs metabolized to amphetamines

At least two additional drugs on the market today are metabolized in part to amphetamines. Neither agent is marketed for use in the treatment of ADHD. Famprofazone (marketed as Gewolen and Gewodin) is a nonsteroidal anti-inflammatory agent available in Taiwan and other countries. Amphetamine and methamphetamine are among its metabolites in humans. Methamphetamine is the major metabolite representing 15% of the original dose (Shin et al., 1998). We did not locate information on possible pregnancy or lactation effects of famprofazone.

Selegiline, also known as L-deprenyl, is a substituted amphetamine used in the treatment of Parkinson's disease and is a levorotatory acetylenic derivative of phenethylamine. A monoamine oxidase inhibitor, selegiline also is used in the treatment of depression. Selegiline is marketed in the U.S. as Emsam® and Zelapar®. Selegiline is metabolized in humans to levomethamphetamine, levamphetamine, and *N*-desmethylselegiline (Bausch Health US, LLC, 2020). Selegiline has been abused as a "smart drug" to enhance cognitive functioning (Schneider, Tariot, & Goldstein, 1994) and has demonstrated the potential for abuse as a stimulant when tested in monkeys (Yasar et al., 2006).

2.4 | Other substituted amphetamines

3,4-Methylenedioxymethamphetamine (MDMA), a drug of abuse commonly known as ecstasy or molly, as well as by other names, is a substituted amphetamine. MDMA actions in pregnancy are not covered by this review, because MDMA is structurally more complex than the amphetamines considered here and is not used for medicinal purposes. Reviews of developmental effects of pregnancy exposures to MDMA are available (e.g., Barenys, Reverte, Masjosthusmann, Gómez-Catalán, & Fritsche, 2019; Skelton, Williams, & Vorhees, 2008). Other substituted amphetamines not covered in this review are ephedrine, cathinone, phentermine, and bupropion. None of these agents are metabolized to amphetamines.

3 | EXPERIMENTAL ANIMAL STUDIES, NONBEHAVIORAL OUTCOMES

Human medicinal exposures to amphetamines are typically oral. Although some developmental studies of amphetamines conducted in experimental animals have been conducted by the oral route of exposure, most studies have used intraperitoneal (i.p.) or subcutaneous (s.c.) administration.

3.1 | Rats

3.1.1 | Amphetamine

Of the three published studies of developmental effects of pregnancy exposures to amphetamines in rats reviewed by Golub et al. (2005), one was an oral study (Ching & Tang, 1986). Gavage administration of dextroamphetamine sulfate at up to 5 mg/kg/day throughout gestation decreased the birth weight and survival of neonatal rats at the highest dose level tested (Ching & Tang, 1986). No data were presented with which to assess the possible presence of maternal toxicity for its potential influence on pup outcomes, and as such, this study was deemed inadequate for the evaluation of developmental effects (Golub et al., 2005). No additional oral studies of amphetamine in pregnant rats have been published since 2005.

Unpublished manufacturer oral studies of amphetamine also have been conducted in pregnant rats. According to information in the U.S. FDA pharmacology review and product labeling for Adderall XR®, when amphetamine was tested in rats using the dextro- to levo-enantiomer ratio of 3:1, it did not adversely affect early embryonic development in the rat when administered by

gavage at up to 20 mg/kg/day given to males and females prior to and during mating and through gestation day (GD) 7 (Center for Drug Evaluation and Research, 2001; Shire US Manufacturing Inc., 2019). Amphetamine, in the enantiomer ratio present in Adderall®, had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats on GD 6–17 at up to 6 mg/kg/day. The high dose level was estimated as twice the maximum recommended human dose of 20 mg/day in adolescents on a mg/m^2 basis.

A study not reported in the U.S. FDA 2001 pharmacology review is described in the 2019 Adderall XR® product labeling (Shire US Manufacturing Inc., 2019). Pregnant rats received daily oral doses of amphetamine (dextro- to levo-enantiomer ratio of 3:1) of 2, 6, or 10 mg/kg/day on GD 6 to lactation day 20. These doses were estimated to represent 0.8, 2, and 4 times, respectively, the maximum recommended human adolescent dose of 20 mg/day on a mg/m^2 basis. Hyperactivity, decreased weight gain in the dams, and decreased pup survival were observed at all dose levels. A decrease in pup body weight at 6 and 10 mg/kg/day was associated with delays in developmental landmarks, including preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg/day on postnatal day (PND) 22 but not at 5 weeks postweaning. Offspring in the high dose group, when tested for reproductive performance, showed decreases in gestational weight gain, number of implantations, and litter size.

According to the product labeling, lisdexamfetamine dimesylate had no adverse effects on embryonic or fetal development or survival when administered orally to pregnant rats on unspecified gestational days at doses of up to 40 mg/kg/day (Shire LLC, 2019). This dose level is four times the maximum recommended human dose of 70 mg/day given to adolescents on a body surface area basis.

Radiolabeled dextroamphetamine administered by intraperitoneal injection at 5 mg/kg to female mice on GD 16 crossed the placenta, with fetal tissues having lower concentrations than maternal tissues (Shah & Yates, 1978).

3.1.2 | Methamphetamine

The offspring of pregnant rats treated orally with methamphetamine 2.5 mg/kg/day on GD 7–21 showed delayed maturation and behavioral delays in the absence of maternal toxicity when compared to unexposed controls and to groups exposed to lower dose levels of methamphetamine (McDonnell-Dowling, Donlon, & Kelly, 2014). An additional study from the same laboratory found that developmental impairments observed with methamphetamine at 3.75 mg/kg/day on GDs 7–21 were exacerbated if the dosing was via the subcutaneous route instead of the oral route (McDonnell-Dowling & Kelley, 2016). Dextromethamphetamine administered by subcutaneous injection twice/day at 15 or 20 mg/kg/day on GDs 7–12 produced anophthalmia/microphthalmia (Acuff-Smith, Schilling, Fisher, & Vorhees, 1996). Folded retina was observed in rats dosed with 20 mg/kg/day on GDs 13–18. In a study where the pregnant dam self-administered methamphetamine by the intravenous route at dose levels of 2–3 mg/kg/day throughout gestation, the exposed pups showed delays in reaching developmental milestones when compared to controls (Rüedi-Bettschen & Platt, 2017). The milestones evaluated included righting reflex, negative geotaxis, pinna detachment, fur appearance, incisor eruption, and eye opening.

3.2 | Mice

Gavaging mice with 50 mg/kg/day amphetamine sulfate throughout gestation increased the prevalence of cleft palate (Yasuda, Ariyuki, & Nishimura, 1967), with a reduction in maternal body weight. No other dose level was tested in this study. Fetal malformations and death have been reported in mice following parenteral administration of dextroamphetamine doses of ≥50 mg/kg/day, approximately six times that of a pediatric human dose of 30 mg/day on a mg/m^2 basis (Teva Pharmaceuticals USA, Inc., 2020). Administration of these dose levels also was associated with severe maternal toxicity. Dextroamphetamine induced ventricular and atrial septal defects, eye defects, cleft palate, and skeletal defects in mice at a single intraperitoneal dose of 50 mg/kg administered on GD 8 (Nora, Sommerville, & Fraser, 1968; Nora, Trasler, & Fraser, 1965). This dose was estimated by the authors as 200 times higher than the typical human dose; labeling from the dextroamphetamine product Dexedrine® Spansule® estimated the dose as approximately 41 times the maximum human dose (Amneal Pharmaceuticals LLC, 2019). No other dose levels were tested in these studies. Methamphetamine produced cleft palate, exencephaly, microphthalmia, and anophthalmia in mice at intravenous dose levels of 5 or 10 mg/kg/day administered for various day ranges during gestation (Kasirsky & Tansy, 1971).

3.3 | Rabbits

In a pharmaceutical company study, dextroamphetamine sulfate did not increase structural malformations in rabbits at 10 mg/kg, with the days and route of dose delivery not

stated (Paget, 1965). Methamphetamine administered intravenously to rabbits at 1.5 mg/kg/day on GDs 12–15, 15–20, or 12–30 produced defects including cyclopia, exencephaly, and microphthalmia (Kasirsky & Tansy, 1971).

3.4 | Conclusions on experimental animal studies, nonbehavioral outcomes

Studies in rats did not show congenital malformations at any dose level, whereas malformations were observed in some mouse and rabbit studies at dose levels higher than typical human exposure levels. In a methamphetamine study conducted in pregnant rats using self-injection, developmental milestones were delayed in the offspring.

4 | BEHAVIORAL EFFECTS OF GESTATIONAL EXPOSURES TO AMPHETAMINES IN EXPERIMENTAL ANIMALS

The 2005 amphetamine review by Golub et al. provided an assessment of 13 neurobehavioral studies of rats exposed only prenatally to amphetamine or dextroamphetamine. A range of behavioral paradigms were used in these studies, including open field testing, dry and water maze performance, operant conditioning, and avoidance testing. Weaknesses of the majority of the studies assessed, as indicated by Golub et al., involved complexities in or limited information on experimental design, too few animals tested, only a single dose tested, and/or lack of information on the purity of the test substance. Three of the studies on amphetamine or dextroamphetamine were considered to be of high quality (Adams, Buelke-Sam, Kimmel, & LaBorde, 1982; Holson, Adams, Buelke-Sam, Gough, & Kimmel, 1985; Vorhees, 1985). All of these studies were conducted with subcutaneous dosing on GDs 12–15 with the highest dose level tested being 2 or 3 mg/kg/day. These three studies found little if any evidence of behavioral teratogenicity. A more recent study in rats was conducted using only one dose level (1 mg/kg) of dextroamphetamine administered s.c. on GDs 11–21 and evaluated locomotor activity in individual cages on PNDs 35 and 60 (Flores, de Jesus Gomez-Villalobos, & Rodriguez-Sosa, 2011). A decrease in locomotor activity compared to controls was observed.

Studies of methamphetamine developmental exposure in rats have shown conflicting results with respect to effects on behavior, depending upon the test system used and time of exposure. There were no effects on cognitive function in adult rats that had been exposed prenatally to methamphetamine at 5 mg/kg/day throughout gestation (Macúchová, Nohejlová, & Slamberová, 2014). Increased impulsivity, compulsivity, and motivation for reward were observed in adult mice exposed prenatally to methamphetamine, also at 5 mg/kg/day throughout gestation (Lloyd et al., 2013).

A series of studies showed that methamphetamine exposure in rats during the equivalent of the human third trimester period of brain development (regarded as the first two postnatal weeks) resulted in deficits in spatial navigation in the Morris water maze, Cincinnati water maze, and the Barnes maze at dose levels as low as 5 or 10 mg/kg/day provided given four times/day s.c. (Acuff-Smith et al., 1996; Vorhees et al., 2008; Vorhees et al., 2009; Williams et al., 2003).

5 | STRUCTURAL MALFORMATIONS IN HUMANS

5.1 | Prescription use

A U.S. population-based case–control study from the National Birth Defects Prevention Study examined the use of prescription amphetamines, methylphenidate, and atomoxetine in pregnancies with an estimated date of delivery between 1998 and 2011 (Anderson et al., 2018). The investigators considered live birth, stillbirth, and miscarriage. Maternal recall was used to identify medication use. Methamphetamine-alone users were excluded. Approximately 32,000 birth defect cases and 12,000 controls were identified. Twenty control mothers and 64 case mothers reported use of an ADHD medication from 1 month prior to conception through the first 3 months of pregnancy. The prevalence of ADHD medication exposure was 0.2% in cases and controls, whether restricted to pregnancy only or to the 3 months prior to conception plus during pregnancy. The combination of amphetamine/dextroamphetamine accounted for 39.8% of all exposures and methylphenidate accounted for 37.8% of exposures. These medication exposures were analyzed together rather than separately. There were few exposures to other medications or atomoxetine. After adjusting for maternal age, an increased risk estimate for gastroschisis was identified, in contrast to 11 other birth defects for which there were at least three exposed cases. The adjusted odds ratio for gastroschisis was 3.0, 95% confidence interval 1.2–7.4. Initial findings for omphalocele and transverse limb defects did not persist after adjustment for maternal age. Individual medication exposure levels for the cases were not presented. Maternal diagnosis was not ascertained and confounding by indication could not be excluded.

A retrospective cohort study using a U.S. Medicaid database of live births from 2000 to 2013 found that filling a prescription for amphetamine or dextroamphetamine consistent with first trimester exposure ($N = 5{,}571$) was not associated with increased risk estimates for any cardiac malformation or total malformations (Huybrechts et al., 2018).

A U.S.-Canadian case–control study of 219 children with congenital heart disease diagnosed by 2 years of age found no difference in the prevalence of prescription dexamphetamine use 30–55 days after the last menstrual period compared to unaffected controls ($N = 153$) (Nora, McNamara, & Fraser, 1967). In the same paper, the authors reported the results of a prospective study of 52 infants with documented exposure to dextroamphetamine between 30 and 55 days after the last menstrual period. There were no congenital heart defects detected by 1 week of age in the exposed group and there were no differences in the prevalence of other malformations compared to 50 unexposed controls.

The prospective U.S. Collaborative Perinatal Project, a cohort study, followed 50,282 pregnant women prospectively and found no increased risk for total malformations among 367 mother–infant pairs exposed to dextroamphetamine and 215 exposed to amphetamine in lunar months 1–4 (Heinonen, Slone, & Shapiro, 1977). A study from the prospective U.S. Child Health Development Studies found no increase in malformations among 347 term infants whose mothers used prescription amphetamines compared to 8,989 unexposed children (Milkovich & van den Berg, 1977).

5.2 | Illicit use

A U.S. case–control study of infants and fetuses with neural tube defects reported risk estimates less than 1 for periconceptual use of amphetamines, other illicit drugs, alcohol, and tobacco. Most of the women used more than one substance and exposure could not be quantified (Shaw, Velie, & Morland, 1996).

A U.K. case–control study of 144 cases of gastroschisis (the majority of which were isolated anomalies) reported an adjusted odds ratio of 3.3, 95% confidence interval 1.0–1.5 for first trimester recreational use of vasoconstrictive drugs (cocaine, amphetamines, or MDMA) based on 10 exposed cases and 6 controls (Draper et al., 2008).

A U.S. case–control study that compared 14 infants with gastroschisis to 57 unaffected controls found an association with pre-pregnancy methamphetamine use, odds ratio 7.15; 95% confidence interval 1.35–37.99, or pre-pregnancy recreational use of any vasoconstrictive drug (cocaine, MDMA, methamphetamine, amphetamine), odds ratio 4.46, 95% confidence interval 1.21–16.44 (Elliott et al., 2009). Maternal self-report was used to identify drug use. All substance-abusing mothers reported cessation of drug use when they discovered that were pregnant.

5.3 | Conclusions on structural malformations in humans

Prescription and illicit amphetamines were associated with gastroschisis is some studies, although one study combined other illicit drugs believed to cause vasoconstriction. Other studies did not find associations with structural malformations including cardiac malformations.

6 | CHILDHOOD GROWTH

The Infant Developmental, Environment, and Lifestyle (IDEAL) study followed cohorts of mothers and infants in the U.S. and New Zealand exposed or unexposed to illicit methamphetamine. A report from the New Zealand site of the IDEAL study found decreases in head circumference, weight, and height at ages 1, 2, and 3 years, respectively, among 103 children exposed to methamphetamine in utero (Wouldes et al., 2014). The IDEAL study is discussed in more detail in Section 8.3.

Infant length and child height at age 3 years were negatively associated with prenatal methamphetamine exposure (Abar et al., 2014). No effect was found for birth weight or child weight after adjustment for potential confounders including maternal weight and country of origin. A statistically significant decrease in height trajectory by an average of 0.63 cm from birth to 3 years was associated with prenatal methamphetamine exposure (Zabaneh et al., 2012).

7 | DISEASES OF ABNORMAL PLACENTAL FUNCTION

Fetal growth restriction, preterm delivery, and preeclampsia have been associated with abnormal placental function, perhaps related to abnormal remodeling of maternal arterioles in the placental bed. Exposure to vasoconstricting drugs including amphetamines in therapy or abuse scenarios might increase the prevalence or severity of these conditions. A 2011 meta-analysis concluded that use of amphetamines during pregnancy was associated with an increase in preterm birth (summary odds ratio 4.11, 95% confidence interval 3.05–5.55), low birth weight (summary odds ratio 3.97, 95% confidence interval 2.45–6.43), and small for gestational age infants

(summary odds ratio 5.79, 95% confidence interval 1.39–24.06), but the diversity of study designs and study quality raises the question of whether meta-analysis was appropriate (Ladhani et al., 2011). Examination of 103 placentas from women who used ethanol, tobacco, marijuana, and/or methamphetamine, ascertained by interview and urine screening, reported heavier placentas and larger placenta: fetal weight ratios associated with methamphetamine use (Carter et al., 2016). Multivariate analysis was used to adjust for other exposures. The authors postulated that methamphetamine-associated placenta hypoxia increased placental growth without effects on fetal growth. There was no increase in histopathological abnormalities in these placentas.

7.1 | Fetal growth

Fetal growth historically has been evaluated using birth weight. A birth weight less than the 10th percentile for gestational age is considered small for gestational age. Birth weight less than 2,500 g is called lowbirth weight, but depending on gestational age, this birth weight may not be abnormal. In addition to gestational age, birth weight is influenced by maternal illness, race, cigarette smoking, ethanol use, and parental body size.

7.1.1 | Prescription use

Women ($N = 237$) using dextroamphetamine for weight control and not for mood effects were ascertained from the Collaborative Perinatal Project, a cohort study, and matched to nonusing women on race, parity, and smoking habits (Naeye, 1983). Data were stratified by maternal pre-pregnancy weight, weight gain at the end of pregnancy, and blood pressure. Term offspring birth weight was lower in all strata for women taking dextroamphetamine after 28 weeks gestation but not for women who stopped treatment by 28 weeks. Adjustment for potential confounding beyond the stratified analysis was not discussed.

Among 53 pregnant women identified in Mayo Clinic medical records as having taken amphetamine-dextroamphetamine for ADHD, there was no difference in the mean birth weight of offspring compared to the offspring of women not taking ADHD medication (Rose, Hathcock, White, Borowski, & Rivera-Chiauzzi, 2020). This study described a retrospective cohort design.

A nationwide Medicaid prescription database study did not identify an association of small for gestational age infants with the mother filling a prescription for amphetamine during the first half of pregnancy based on 3,331 amphetamine/dextroamphetamine-exposed women (Cohen et al., 2017). A database linkage study in Sweden identified 1,591 women with a prescription for ADHD medication during pregnancy, 9,475 women with a prescription for ADHD medication before or after but not during pregnancy, and 953,668 women with no prescription for ADHD medication (Nörby, Winbladh, & Källén, 2017). Methylphenidate accounted for about 90% of the ADHD medication. Other medications included amphetamine, dextroamphetamine, lisdexamfetamine, and atomoxetine. ADHD medications were reported to be associated with an increase in large for gestational age infants, but the finding was not statistically significant and results were not separately reported for amphetamines. No conclusions on amphetamines are possible based on this study. These database investigations were structured as cohort studies.

7.1.2 | Illicit use

Clinical studies have used convenience samples of presumably exposed pregnancies. Among 70 Swedish women considered addicted to "amphetamine" based on patient interview, midwife report, and information from social services, 17 reported stopping drug use when they learned they were pregnant, and 53 continued drug use (Eriksson, Larsson, & Zetterström, 1981). The specific amphetamines were not discussed. Small for gestational age infants were born to 7 of 52 women with continued exposure (counting twins as separate events). One of the 17 pregnancies in abstainers resulted in a small for gestational age infant. No statistical methods were discussed, and there was no consideration of use of ethanol or other drugs. Among 106 pregnant women positive for amphetamine by universal screening in labor at the University of California, Davis, there was a decrease in birth weight but not in gestational age (Gillogley, Evans, Hansen, Samuels, & Batra, 1990). Demographic information and use of other drugs were reported only for all toxicology screen-positive women, precluding analysis for amphetamine-positive women.

In 52 pregnancies in Dallas, maternal self-reported methamphetamine abuse, primarily by the intravenous route, was associated with a 10% decrease in birth weight, a 3% decrease in length, and a 2% decrease in head circumference compared to nonabusing women from the same obstetric unit (Little, Snell, & Gilstrap 3rd., 1988). Although statistically significant, these alterations may not be clinically important. The methamphetamine-abusing women used more tobacco, alcohol, and other illegal drugs, and it is not clear how, if at all, the authors adjusted for this use or for possible differences in race,

prenatal care, nutrition, or poverty. A report from a hospital in the Bangkok area indicated that birth weight and head circumference for gestational age were reduced in newborns of 47 methamphetamine-abusing women, identified through maternal interview and infant urine toxicology screening (Chomchai, Na Manorom, Watanarungsan, Yossuck, & Chomchai, 2004). There was no adjustment for other factors that may have influenced gestational age.

Among 134 Los Angeles women identified by urine toxicology screening and self-report as abusing methamphetamine, there were no differences from a nonusing control group in mean birth weight, length, head circumference, or ponderal index, which is weight divided by length-cubed (Smith et al., 2003). More infants in the methamphetamine group were small for gestational age, defined in this study as weighing less than the fifth percentile. Nicotine use, which was more prevalent among methamphetamine-using women, might have explained these findings.

The IDEAL study recruited mother-infant pairs in the United States and New Zealand. Dyads were considered to have been exposed or unexposed to illicit methamphetamine based on maternal self-report and neonatal meconium screening. Women may have used ethanol, tobacco, or marijuana, but users of opioids, LSD, phencyclidine, or cocaine were excluded. In a sample of 84 women (204 in a follow-up study) from four U.S. sites, the prevalence of small for gestational age infants among methamphetamine abusers was two to three times that in 1,534 unexposed pregnancies (3,501 in the follow-up study) after adjustment for potential confounders (Nguyen et al., 2010; Smith et al., 2006). No difference in prevalence of small for gestational age infants was seen in women discontinuing methamphetamine use by the third trimester.

Small for gestational age infants were not more prevalent among 154 methamphetamine abusers identified by questionnaire and urine drug screening in a Honolulu clinic (Wright, Schuetter, Tellei, & Sauvage, 2015). A Canadian study of socioeconomic status as a mediator of poor pregnancy outcome reported that amphetamine use, presumably illicit, was the most important factor associated with low-birth weight in the sample (Campbell et al., 2018). There were 18 women determined by an unstated method to be amphetamine users, producing a statistically significant but unstable risk estimate, adjusted odds ratio 17.51, 95% confidence interval 1.45–211.04. Based on medical record review, there was a higher prevalence of small for gestational age infants among the offspring of 128 women in Bangkok considered to be amphetamine abusers compared to 256 nonabusing women, crude odds ratio 14.7, 95% confidence interval 4.0–63.8 (Phupong & Darojn, 2007).

A national hospital discharge register was used to define a retrospective cohort study and identified an association between an amphetamine abuse diagnosis and a diagnosis of poor fetal growth, not otherwise defined (Cox, Posner, Kourtis, & Jamieson, 2008). There were an estimated 36,062 hospitalizations with a diagnosis of amphetamine abuse, but the number of individual patients could not be determined. This survey did not adjust for exposure to cigarettes, alcohol, or other substance use unless a use disorder was identified as a discharge diagnosis. Using California birth certificate records and a hospital discharge diagnosis of methamphetamine use, abuse, or addiction, a retrospective cohort study reported an association between drug use and birthweight below 2,500 g, adjusted odds ratio 3.5, 95% confidence interval 3.3–3.8 (Gorman, Orme, Nguyen, Kent III, & Caughey, 2014). There were 8,542 pregnancies identified as methamphetamine exposed. The decrease in birthweight may have been due to preterm delivery.

7.2 | Preterm delivery

Preterm delivery is defined as delivery prior to 37 completed weeks of gestation, counting from the first day of the last menstrual period. A distinction can be made between spontaneous preterm delivery and so-called indicated preterm delivery, the latter being occasioned by induction or cesarean section for pregnancy complications.

7.2.1 | Prescription use

Preterm birth was not associated with filling a prescription for amphetamines in the first half of pregnancy in a nationwide Medicaid database retrospective cohort study; however, in a sensitivity analysis, filling two or more prescriptions showed an association, adjusted relative risk 1.16, 95% confidence interval 1.06–1.35, based on 3,331 amphetamine/dextroamphetamine-exposed women (Cohen et al., 2017). Potential confounders were adjusted using propensity score stratification, and atomoxetine was used as a nonstimulant negative control to identify possible confounding by indication. There was a stronger association in pregnancies where prescription filling continued into the second half of pregnancy. An Australian database linkage study identified 175 women with a possible legal prescription for a stimulant for ADHD (Poulton, Armstrong, & Nanan, 2018). Two-thirds of prescriptions were for dextroamphetamine and the remainder was for methylphenidate. There was no association in

adjusted analysis between use of a stimulant drug during pregnancy and delivery prior to 37 weeks. A database linkage study, also a retrospective cohort, in Sweden identified 1,591 women with a prescription for ADHD medication during pregnancy, 9,475 women with a prescription for ADHD medication before or after but not during pregnancy, and 953,668 women with no prescription for ADHD medication (Nörby et al., 2017). Methylphenidate accounted for about 90% of the ADHD medication. Comparing women using and not using ADHD medication during pregnancy, there was an association of ADHD medication with delivery at 32–36 weeks, adjusted odds ratio 1.3, 95% confidence interval 1.1–1.6. There was no increase in deliveries prior to 32 weeks. No conclusions are possible about amphetamines based on this study.

7.2.2 | Illicit use

Clinical studies used convenience samples of patients or patient records. In a sample of 70 Swedish women considered addicted to unidentified amphetamine based on patient interview, midwife report, and information from social services, 17 reported that they stopped drug use when they learned they were pregnant and 53 continued drug use (Eriksson et al., 1981). Preterm delivery occurred in 13 of the 53 continuing users compared to 1 of the 17 abstainers. No statistical methods were discussed, and there was no consideration for use of ethanol or other drugs. Based on medical record review, there was a higher prevalence of preterm delivery among 128 Bangkok women considered to be amphetamine abusers compared to 256 nonabusing women, crude odds ratio 4.4, 95% confidence interval 2.3–8.6 (Phupong & Darojn, 2007).

Twenty-eight pregnant women in San Diego identified by urine toxicology screening as having abused methamphetamine but no other drugs were combined for analysis with 18 women who abused cocaine with or without methamphetamine, precluding the identification of possible methamphetamine effects (Oro & Dixon, 1987). In the combined group, there was more than a threefold increase in preterm delivery.

There was a 6% decrease in gestational age among offspring of 134 women identified as methamphetamine abusing by urine toxicology screening and self-report compared to a nonusing population in Los Angeles (Smith et al., 2003). None of the infants in either group were born prior to 37 weeks gestation, because delivery at term was one of the inclusion criteria for this study.

In a chart review study in a Phoenix hospital, preterm delivery was identified among 52% of 276 births to women identified by urine toxicology screening as methamphetamine users compared a 17% prevalence in a general obstetric population (Good, Solt, Acuna, Rotmensch, & Kim, 2010). The reliability of this comparison is low given potentially important differences between the populations in employment, ethnicity, prenatal care, and marital status, differences in use of nicotine, ethanol, and marijuana, the nonsystematic application of urine toxicology screening, and the documentation of domestic violence in 23% of methamphetamine-using women. Among 50 Australian women considered in hospital records to be abusing mainly amphetamines, 26% delivered prior to 57 weeks gestation compared to 7.9% in the Western Australia general population, a statistically significant difference in unadjusted analysis (Ludlow, Evans, & Hulse, 2004).

In selected U.S. sites from the IDEAL cohort study, gestational age was about 10% lower among methamphetamine-exposed compared to unexposed pregnancies adjusted for potential confounders (Nguyen et al., 2010). Among methamphetamine abusers identified by questionnaire and urine drug screening in a Honolulu clinic, there was an association with delivery prior to 37 weeks only among the 157 women who had positive screens at delivery compared to women considered not to be illicit drug-users, adjusted odds ratio 3.54, 95% confidence interval 1.02–11.66 (Wright et al., 2015).

Administrative database studies of nationwide U.S. or statewide California hospital discharges reported an association between a diagnostic code for amphetamine abuse and preterm birth (Cox et al., 2008, $N = 36{,}062$ hospitalization; Gorman et al., 2014, $N = 8{,}542$; Baer et al., 2019, $N = 48{,}133$). These investigations were structured as retrospective cohort studies. In one of the California samples, the adjusted relative risk for preterm birth before 32 weeks was 4.5, 95% confidence interval 4.0–5.1 (Gorman et al., 2014); for delivery before 37 weeks, the adjusted odds ratio was 2.9, 95% confidence interval 2.7–3.1. There were 8,542 pregnancies identified as methamphetamine exposed in this study.

7.3 | Preeclampsia and placental abruption

Preeclampsia historically was defined as hypertension, proteinuria, and edema after 20 weeks gestation; however, more recent definitions do not require all three elements to be present. Eclampsia is preeclampsia complicated by maternal seizure or coma. Preeclampsia is characterized by segmental arteriolar spasm and vascular leaks resulting in hemoconcentration as fluid leaves the intravascular compartment for tissue spaces including the lung. Gestational hypertension is elevated blood

pressure during pregnancy and may be related pathophysiologically to preeclampsia. The prevalence of preeclampsia increases with extremes of maternal age, a personal or family history of preeclampsia, and among women having their first child.

Placental abruption is premature separation of the placenta, sometimes a complication of preeclampsia or other hypertensive disorders. Placental abruptions can result in labor, maternal hemorrhage and death, and fetal hypoxia or death.

7.3.1 | Prescription use

Blood pressure was not increased among 237 women from the Collaborative Perinatal Project cohort study if the women took dextroamphetamine for weight control compared to women believed not to be using amphetamines (Naeye, 1983). A database linkage retrospective cohort study in Australia identified 175 women with a possible legal prescription for a stimulant for ADHD (Poulton et al., 2018). Two-thirds of prescriptions were for dextroamphetamine and the remainder was for methylphenidate. There was no association in adjusted analysis between use of a stimulant drug during pregnancy and preeclampsia. Preeclampsia was associated with filling a prescription for amphetamine in the first half of pregnancy in a nationwide Medicaid database retrospective cohort study; the relative risk adjusted using propensity score was 1.2, 95% confidence interval 1.12–1.58, based on 3,331 amphetamine/dextroamphetamine-exposed women (Cohen et al., 2017). There was no increase in placental abruption. Atomoxetine, a nonstimulant medication for AHDH, showed no association, suggesting that confounding by indication was not involved. Prescription amphetamine use after 20 weeks gestation was identified in 12 women in a case–control study of hypertensive disorders of pregnancy (Newport et al., 2016). On post hoc exploratory analysis, women with hypertensive disorders took a higher mean daily dose of amphetamine (33.8 mg/day) compared to women without these disorders (16.3 mg/day).

7.3.2 | Illicit use

Clinical studies used convenience samples of patients or medical records. Pregnancy-induced hypertension was reported in four of 52 self-identified methamphetamine-abusing women in Dallas compared to seven of 52 women believed not to have abused illicit drugs (Little et al., 1988). These proportions were not statistically different. Among 70 amphetamine addicts in Sweden, 17 reported stopping drug use when they learned they were pregnant and 53 continued drug use (Eriksson et al., 1981). Elevated blood pressure on at least one occasion occurred in 6 of the 53 continued users and none of the abstainers, and proteinuria occurred in 9 of the continued users and 1 of the abstainers. No statistical methods were discussed and there was no consideration of use of ethanol or other drugs. Based on review of the medical records of 128 women in Bangkok considered to be amphetamine abusers compared to 256 nonabusing women, there was no difference in the prevalence of preeclampsia (Phupong & Darojn, 2007). Among 144 methamphetamine-abusing women in Honolulu, neither preeclampsia nor chronic hypertension was increased compared to women not using illicit drugs (Wright et al., 2015).

A national hospital discharge register used to constitute a retrospective cohort study identified an association between an amphetamine abuse diagnosis and hypertension complicating pregnancy (Cox et al., 2008). This survey did not adjust for exposure to cigarettes, alcohol, or other substance use unless a use disorder was identified as a discharge diagnosis. There was also an association between amphetamine abuse and placental abruption. Because the register counted hospitalization and not individual patients, women with multiple hospitalizations would have been overcounted. A database linkage study using California birth certificate records and a hospital discharge diagnosis of methamphetamine use, abuse, or addiction identified an association with a diagnosis of pregnancy-associated hypertension, preeclampsia, eclampsia, placental abruption, and neonatal death (Gorman et al., 2014). There were 8,542 pregnancies identified as methamphetamine exposed. After regression analysis, associations for methamphetamine abuse included: preeclampsia, adjusted odds ratio 2.7, 95% confidence interval 2.4–3.0; eclampsia, adjusted odds ratio 4.4, 95% confidence interval 2.6–7.3; gestational hypertension, adjusted odds ratio 1.8, 95% confidence interval 1.6–2.0; and placental abruption adjusted odds ratio 5.5, 95% confidence interval 4.9–6.3.

7.4 | Conclusions on placenta-related diseases

Prescription use of amphetamines has not been associated with deficits in birth weight in retrospective cohorts. An increase in preterm delivery or a decrease in gestational age at delivery was identified. Illicit use of amphetamines was associated with a decrease in birth weight and an increase in preterm delivery in some studies, although many of these studies were convenience

samples of clinical records. Most studies did not associate prescription amphetamine use with preeclampsia, but a prescription database study using a retrospective cohort design reported a statistically significant 1.2-fold increase in hypertensive disorders in pregnant women filling a prescription for amphetamine or dextroamphetamine. Most of the available reports identified an association between illicit use of amphetamines, chiefly methamphetamine, and hypertensive disorders of pregnancy.

8 | NEURODEVELOPMENTAL AND NEUROBEHAVIORAL EFFECTS OF AMPHETAMINE PREGNANCY EXPOSURES IN CHILDREN

8.1 | Structural effects on brain development

Studies on structural effects on the brain have been conducted in children whose mothers abused amphetamines during pregnancy. None of these studies adequately adjusted for potential confounders.

The effects of prenatal exposure to methamphetamine on childhood brain development were studied in a convenience sample of 13 exposed children (Chang et al., 2004). The average age of the children was approximately 7 years with a range of 3–16 years. The mothers of these children reported that they did not have dependence upon alcohol (although some reported light alcohol use) or other illicit drugs. Compared to control children, magnetic resonance imaging (MRI) revealed that the exposed children had smaller subcortical volumes. No differences between exposed and control children were observed in thalamus, midbrain, or cerebellum volumes. The exposed children also had deficits in visual motor integration, verbal and long-term spatial memory, and attention when compared to controls.

A convenience sample of children ages 7–15 was studied using functional MRI (Roussotte et al., 2011). Fifteen of the children were exposed to both methamphetamine and alcohol prenatally, 4 were exposed to methamphetamine alone, 13 were exposed to alcohol alone prenatally, and 18 were prenatally unexposed. During visuospatial working memory tests, the group exposed to methamphetamine with or without alcohol showed decreased activation in striatal and frontal regions of the left hemisphere, as well as other brain regions, compared to the control group. The alcohol-alone group showed a level of activation of those same brain regions that was between that of the methamphetamine and alcohol group and the control group. A follow-up study in the same children (Roussotte et al., 2012) showed increased connectivity between the putamen and frontal brain regions and decreased connectivity between the caudate and frontal brain regions. These findings suggested to the authors that damage to the frontostriatal circuit caused by in utero exposure to methamphetamine prevented access to that brain region during the working memory task, which could have resulted in a rewiring of corticostriatal networks. The data for the four children exposed to methamphetamine alone were presented only in combination with the children exposed to both methamphetamine and alcohol. The presence of alcohol exposure among most of the children with methamphetamine exposure makes the methamphetamine contribution to the results difficult to interpret.

A diffusion tensor imaging study of white matter changes in the striatal-orbitofrontal circuit in a convenience sample of neonates after prenatal methamphetamine exposure found that increasing methamphetamine exposure was associated with reduced fractional anisotropy in connections between the striatum and midbrain, orbital frontal cortex, and associated limbic structures after adjustment for confounders (Warton et al., 2018). Higher fractional anisotropy is associated with healthy and highly structured white matter, so reduced fractional anisotropy suggests a white matter deficiency. The changes observed with methamphetamine exposure may play a role in the deficits observed in attention and inhibitory control seen in children with prenatal methamphetamine exposure.

Diffusion tensor imaging along with neurocognitive testing was conducted with a group of children at approximately 10 years of age (Colby et al., 2012). Seventeen of 21 children with prenatal exposure to methamphetamine were also exposed prenatally to alcohol. Nineteen children were exposed prenatally to alcohol alone and the exposed children were compared to 27 children referred to as "typically developing." Children with methamphetamine exposure with or without alcohol showed higher fractional anisotropy in left-sided brain regions compared to the control children. Children with prenatal exposure to alcohol alone had lower fractional anisotropy in frontotemporal regions compared to the methamphetamine with or without alcohol group. The results suggested to the authors that there were changes in brain microstructure that were unique to children with methamphetamine exposure when compared to children with alcohol exposure, and, moreover, that these changes persisted to the age of 10. The study methods did not suggest that methamphetamine or alcohol exposures that may have occurred during lactation were considered.

A diffusion tensor imaging study was conducted in a convenience sample of children 6–7 years of age (Roos et al., 2015). Seventeen of the children had been exposed

to methamphetamine prenatally, and the analyses were adjusted for maternal use of nicotine. Poor motor coordination and executive function was observed in exposed children, along with disruptions of white matter structural integrity in striatal, frontal, and limbic brain regions.

An MRI study was conducted in a cohort of 6-year-olds with in utero methamphetamine exposure and compared to unexposed controls (Roos, Jones, Howells, Stien, & Donald, 2014). Among exposed children of both sexes, there was evidence of increased left putamen volume and reduced left hemisphere cortical thickness when compared to controls. Effects of sex in exposed children were also found on cortical volume and thickness by brain region.

Cohorts of children age 3–4 years old were evaluated by MRI without sedation and with a neuropsychological test battery (Chang et al., 2009). Forty-nine of the children were exposed in utero to methamphetamine and there were 49 control children. These children were similar in terms of physical characteristics including head circumference. They also performed similarly on a Stanford–Binet test of global cognitive function and had parents with similar education, intelligence, mood, and socioeconomic status. The methamphetamine exposed children had poorer performance on a visual motor integration task than control children. The methamphetamine-exposed children had higher total creatine, *N*-acetyl compounds, and glutamate plus glutamine concentrations in the frontal white matter, suggesting higher neuronal density or cellular compactness. The exposed children also had lower myo-inositol concentrations in the thalamus compared to control children, suggesting lower glial content in the thalamus.

8.2 | Behavioral and cognitive effects

Studies of the neurodevelopmental effects of prenatal amphetamine exposure have been conducted in children exposed to amphetamine or methamphetamine abuse during gestation. We did not locate published reports on the offspring of women who used amphetamines for medicinal purposes. Women who abuse amphetamines and methamphetamine may have comorbid use of nicotine, alcohol, marijuana, cocaine, and opioids, and pregnancies may be complicated by malnutrition, domestic violence, history of childhood abuse, poverty, and poor prenatal care. Studies did not adequately address maternal or paternal mental health, the effects of caregiver mental health, or exposure to early childhood adversity in the postnatal environment. Each outcome study is subject to limitations that preclude assignment of a causal relationship for negative effects to illicit amphetamine or methamphetamine exposure alone.

A cohort of 71 children born in Sweden between 1976 and 1977 to 69 women who abused amphetamines during pregnancy (either restricted to the first trimester or throughout pregnancy) was identified at birth (Eriksson et al., 1981; Larsson, Eriksson, & Zetterström, 1979) and followed up to 14 years of age (Cernerud, Eriksson, Jonsson, Steneroth, & Zetterström, 1996). The majority of the women used alcohol and tobacco during pregnancy (Eriksson, Billing, Steneroth, & Zetterström, 1989) and some used heroin, LSD, and/or barbiturates (Larsson et al., 1979). In addition, 65 children survived to 1 year of age, and 12 had impaired emotional development defined as lack of stranger anxiety, autism, or speech delays of the children (Billing, Eriksson, Larsson, & Zetterström, 1980). Most of the affected children lived primarily with mothers who continued to abuse drugs, and nine had fine or gross motor delays. At age 4 years, 24 of the children were judged by a psychologist to have "disturbed" or "problematic" emotional and behavioral development, a finding that was not necessarily associated with the assessments at age 1 year that had been conducted by the same psychologist (Billing, Eriksson, Steneroth, & Zetterström, 1985). Among the factors that were associated negatively with child development were the duration of maternal drug and alcohol use during pregnancy and the number of paternal criminal convictions, regardless of whether the child had contact with the father (Billing, Eriksson, Steneroth, & Zetterström, 1988).

At 8 years of age, peer-related problems and aggressive behaviors were more prevalent in the children of women who abused amphetamines throughout pregnancy (Eriksson et al., 1989) and there was an association with the estimated number of amphetamine injections and the number of months used in pregnancy and an inverse association with a negative attitude toward the pregnancy (Billing, Eriksson, Jonsson, Steneroth, & Zetterström, 1994). Performance at age 14 in Swedish language, mathematics, and physical training was below the mean levels for each child's school, with 10 out of 64 children one grade lower than expected and 8 children in alternative placements (Cernerud et al., 1996). The majority of the children had not lived with their mothers for the entire time since birth, leading investigators to conclude that prenatal amphetamine exposure had a greater influence than postnatal environment on long-term development.

A U.S. cohort study reported the results of cognitive testing in 3- to 4-year-old children who had been exposed to methamphetamine during pregnancy ($N = 49$) as ascertained by maternal report or meconium screening in comparison to a control group of 49 unexposed children

and found no differences except for performance on a test of visual motor integration (Chang et al., 2009). The finding may have been due to chance as there was no adjustment for multiple comparisons.

Investigators in Oregon recruited a community sample of children aged 7–9 years exposed in utero to methamphetamine ($N = 31$), compared them to a group of age-matched unexposed controls ($N = 35$), and found that while cognitive and behavioral assessments by clinicians revealed no clinically significant differences, parental ratings of executive function using the Behavior Rating Inventory of Executive Function indicated greater disturbance in exposed children (Piper et al., 2011). Exposure was determined by maternal or caregiver recall. These investigators also recruited a community sample in the western United States of adopted children and their adoptive parents and biological children living with their biological mothers and conducted two online studies, one using the Behavior Rating Inventory of Executive Function and the other the Child Behavior Checklist to assess the impact of prenatal methamphetamine exposure on cognition and behavior (Piper, Gray, Corbett, Birkett, & Raber, 2014). The children ranged from 5 to 18 years of age and there may have been overlap between the two groups. In the first study, there were 59 adopted children and 378 comparison children, and in the second study, there were 54 adopted children and 495 comparison children. Methamphetamine exposure was determined by adoptive or biological parent recall. Based on parental ratings, the methamphetamine-exposed children were more likely to have difficulties with executive function and with internalizing and externalizing behaviors. The wide age range and lack of clinician ratings were limitations of the study.

Fifteen neonates recruited between 2004 and 2007 for a cohort study in South Africa on the neurodevelopmental effects of prenatal methamphetamine exposure were compared to a control group of 21 unexposed children (van Dyk, Ramanjam, Church, Koren, & Donald, 2014). Children were excluded if the mother had used illicit drugs besides methamphetamine but alcohol and tobacco exposure were permitted. Methamphetamine exposure was determined based on chart reviews and parental interviews. The investigators were not able to determine the quality or quantity of drug, alcohol, or tobacco exposure. The children in each group were evaluated between age 2 and 4 years by an unblinded clinician using the Griffiths Mental Development Scales, and the exposed children had deficits in the subscales for personal-social abilities, eye and hand coordination, and total general performance score. Evaluation of children from 2 to 4 years of age included a wide developmental range. This wide range and the lack of blinding of the examiner detract from the utility of this study.

In a South African cohort study that recruited 6- to 7-year-old children from an elementary school, there were 25 children with prenatal methamphetamine exposure based on maternal/caregiver recall and 22 unexposed controls (Kwiatkowski et al., 2018). The exposed children had poorer performance on tests of IQ, learning and memory, visual-motor integration, and fine motor coordination after adjustment for maternal education and other potential confounders.

A cohort of pregnant women who abused methamphetamine was recruited in Western Australia and neurodevelopment was assessed in the offspring (O'Connor et al., 2020). There were 65 children born either at term or preterm who were evaluated between 10 and 21 months of age (average age 13 months) using the Griffiths Mental Development Scales. Lower scores on general quotient and all subscales were found for the 48 full-term offspring compared to a group of 443 historical controls. Of the 65 children, the majority had been exposed to alcohol and tobacco and 20% to polysubstance abuse, half came from socially disadvantaged Aboriginal families, and most were being followed by child protection and family support services. The extent of self-reported maternal methamphetamineuse was not associated with developmental delays. There was no adjustment for parental education, IQ, or psychiatric illness.

8.3 | IDEAL study

The IDEAL cohort study was a multicenter project that recruited patients in 2002–2004 in U.S. cities believed to have a high prevalence of methamphetamine use: Los Angeles, Des Moines, Tulsa, and Honolulu (Arria et al., 2006; Smith et al., 2006). Maternal exposures were ascertained by self-report and/or infant meconium screening for methamphetamine, amphetamines, or MDMA. Nearly all of the use involved methamphetamine. Use of ethanol, tobacco, and marijuana was included but women abusing only opioids, hallucinogens including LSD, phencyclidine, or cocaine were excluded. Women younger than 18, institutionalized for cognitive or emotional disability, with a history of psychosis, or not speaking English also were excluded. Infants were excluded for multiple birth, critical illness, congenital viral or parasite infection, or chromosome abnormality, and the study included only one infant from a sibship. A comparison group of women not using methamphetamine or other amphetamines was included.

A comparison of 204 women who used methamphetamine during pregnancy with 208 nonusers showed lower socioeconomic status and income in the users (Shah et al., 2012). Users were less likely to have a partner, had fewer prenatal visits, came for prenatal care later in the pregnancy, gained more weight in pregnancy, and were more likely to use tobacco, ethanol, and marijuana. Exposed infants were more likely to have autonomic symptoms, including poor or excessive suck and jitteriness, and were more likely to be admitted to the neonatal intensive care nursery. Exposed infants were less likely to be breastfed and were more likely to be referred to Child Protective Services. Many of these differences were considered as potential confounders in subsequent analyses.

A subset of infants was evaluated within the first 5 days of life using the Neonatal Intensive Care Unit Network Neurobehavioral Scale. An initial cohort of 74 methamphetamine-exposed and 92 unexposed infants in an adjusted analysis showed more physiological stress among exposed infants (Smith et al., 2008). This finding might have been influenced by the lack of adjustment for multiple comparisons in the study. A determination of maternal depression during the first postpartum month showed an association with decreased infant arousal, hypotonicity, and physiological stress with an interaction of methamphetamine exposure and maternal depression (Paz et al., 2009). At 1 month of age, there were no differences in the Neonatal Intensive Care Unit Network Neurobehavioral Scale in the methamphetamine-exposed compared to unexposed groups (Kiblawi et al., 2014).

Child temperament was evaluated at up to 3 years of age in 204 methamphetamine exposed children and 208 controls (Derauf et al., 2011). The Child Behavior Checklist was completed by caregivers when the child was 36 months of age. The Bayley Scales of Infant Development, Second Edition and Preschool Language Scale, Fourth Edition also were administered at this age. Temperament assessed by parent report at 12 months and caregiver psychological and intelligence testing were assessed. In a linear regression model, prenatal methamphetamine exposure did not make an independent contribution to auditory comprehension, expressive communication, total language, mental development index, or psychomotor development index. The Child Behavior Checklist showed no independent contribution of prenatal methamphetamine exposure to internalizing, externalizing, or total problems.

In a separate report on the Peabody Developmental Motor Scales in 278 children and the Bayley Scales of Infant Development in 281 children in this population at 3 years of age, there were no adverse effects of prenatal methamphetamine exposure on cognition (Smith et al., 2011). Subtle fine motor decrements identified at 1 year of age had resolved by 3 years. Administration of the Child Behavior Checklist to caretakers was repeated when the child was 5 years old, although some of the caretakers had changed (LaGasse et al., 2012; Twomey et al., 2013). Children who had been exposed to methamphetamine prenatally were more likely to have anxious/depressed traits reported in adjusted analyses. Evaluating the effects of age, there were more externalizing and ADHD problems at 5 than at 3 years of age, attributed to a decrease in these problems in the comparison group rather than an increase in the methamphetamine-exposed children. Self-reported heavy methamphetamine use during pregnancy was associated with attention problems and withdrawn behavior compared to children exposed to lighter use or no use. Caregiver psychopathology and home environment appeared to exert the strongest influence on child behavior.

At 5.5 years of age, 204 methamphetamine-exposed children and 208 unexposed controls were assessed for symptoms of ADHD using the Conners' Kiddie Continuous Performance Test II (Kiblawi et al., 2013). Methamphetamine-exposed children were more likely than unexposed children to have a score suggesting risk of developing ADHD. There was no distinction according to self-reported heavy use versus any use of methamphetamine during pregnancy. At 7.5 years of age, children were evaluated by caregivers using the Conners' Parent Rating Scale–Revised Short Form (Diaz et al., 2014). Methamphetamine-exposed children scored higher in the cognitive problem subscale but not in subscales for oppositional behavior, hyperactivity, or in the ADHD index after adjustment.

At 5.5 years of age, 26 children with heavy prenatal methamphetamine exposure, as assessed by the mothers, 107 children with “some” methamphetamine exposure, and 130 unexposed children were assessed with tests of executive function including inhibitory control (Derauf et al., 2012). After adjustment for exposure during pregnancy to cigarettes, ethanol, and marijuana, child sex, socioeconomic status, caregiver IQ, Child Protective Services report of physical or sexual abuse, and caregiver psychological symptoms, heavy compared to no methamphetamine exposure was associated with a decrease in correct responses but not a decrease in reaction time on tests of inhibitory control. There were no test differences when comparing some versus no methamphetamine use during pregnancy. At 7.5 years of age, children were evaluated by caregivers using the Child Behavior Checklist and by an index of early life adversity based on study records (Eze et al., 2016). Prenatal methamphetamine exposure was associated with more early life adversity, extreme poverty, and change in caregiver. Methamphetamine-exposed children were reported to have more externalizing, rule-

breaking, and aggressive behavior that appeared to be mediated by early life adversity. An independent effect of methamphetamine on the behaviors was not demonstrated.

New Zealand sites in and around Auckland were added to the IDEAL study in 2006 and recruitment occurred until 2010. The protocol was the same as in the U.S. sites except that women could participate beginning at age 17.5 (the legal age of consent in New Zealand), and non-English speakers who spoke Maori were accepted. The New Zealand site also accepted some methamphetamine-using women who also used opioids. In the U.S. sites, methamphetamine unexposed women were pair matched to exposed women; in New Zealand, group matching was used. Evaluation of 175 U.S. infants and 83 New Zealand infants with the Neonatal Intensive Care Unit Network Neurobehavioral Scale showed decreased quality of movement and increased stress in both populations (LaGasse et al., 2011). Other abnormalities appeared only in the New Zealand sample.

Children from the New Zealand sample were evaluated with the Bayley Scales of Infant Development, Second Edition or the Peabody Developmental Motor Scales, Second Edition at 1, 2, or 3 years of age (Wouldes et al., 2014). There were 103 children exposed prenatally to methamphetamine and 107 control children. Children prenatally exposed to methamphetamine had lower scores on the Bayley Scale Psychomotor Development Index and the Peabody Developmental Motor Scales among boys.

8.4 | Conclusions on neurodevelopmental effects in humans

Neurodevelopmental research conducted in children exposed in utero to amphetamine and methamphetamine abuse has not yielded consistent findings in brain imaging studies or in cognitive, behavioral, or emotional domains. No study has adequately controlled for confounders such as antenatal exposure to other illicit or licit substances; exposure to neurobiological stressors such as poverty, domestic violence, child abuse, or parent or caregiver neurobiological disorders; or paternal and maternal cognitive function. We have not located studies on the offspring of women who used amphetamines for therapeutic purposes.

9 | LACTATION

Adult rats exposed to methamphetamine in utero via s.c. dosing to the dam of 5 mg/kg/day for 3 weeks prior to fertilization, throughout gestation, and via milk on PNDs 9–20 had behavioral changes in locomotion (males) and exploratory behavior (males and females) that were attributed to the lactational exposure alone (Hrubá, Schutová, & Šlambrová, 2012). Rat pups exposed to methamphetamine via nursing from dams dosed with 3.75 mg/kg/day on PNDs 1–21 demonstrated impairments in both somatic and behavioral development (McDonnell-Dowling & Kelly, 2015).

Amphetamines are excreted in human milk. In a woman taking racemic amphetamine for narcolepsy during breastfeeding, the mean milk/maternal plasma concentration ratio for amphetamine was 3 (Öhman, Wikner, Beck, & Sarman, 2015). The infant had a plasma concentration of about 9% of the maternal plasma concentration, while the infant dose of amphetamine was estimated to be 2% of the mother's daily dose of 35 mg. No adverse effects of amphetamine exposure were observed in the infant, and development was normal through 10 months of age.

Dextroamphetamine was given orally to four nursing mothers for treatment of ADHD (Ilett, Hackett, Kristensen, & Kohan, 2007). The infants had been breastfed since birth, and ages ranged from 3.3 to 10 months at the time of the report. The mothers had been taking a range of 15–45 mg of dextroamphetamine for 2–60 months, suggesting that it was taken by some women during pregnancy. The average infant dose was 21 μg/kg/day, with a range of 11–39 μg/kg/day. No adverse effects on infant development were observed.

Methamphetamine and amphetamine were detected in the milk of two lactating women using methamphetamine by the intravenous route (Bartu, Dusci, & Ilett, 2009). The calculated infant dose of methamphetamine via milk to the infants would have been 16.7 and 42.2 μg/kg/day, although the infants were not breastfed during the 24 hr of the pharmacokinetic study.

In two lactating mothers who smoked methamphetamine and had positive urine drug screens for methamphetamine at delivery, timed milk samples were obtained for analysis while the women were hospitalized postpartum (Chomchai, Chomchai, & Kitsommart, 2016). The half-life values for methamphetamine in the milk samples taken from the first 24 hr of lactation of the two women were calculated as 11.3 and 40.3 hr. The estimated infant doses over that same time period were 21.3 and 51.7 μg/kg/day. Methamphetamine was undetectable in milk approximately 100 hr after the last exposure, but urine samples remained positive for an additional 30–75 hr. The infants were not breastfed.

In conclusion, amphetamine and dextroamphetamine entered milk, but no adverse effects were reported in nursing infants. Studies of methamphetamine in lactating rats found adverse behavioral effects in nursing pups.

Studies of methamphetamine in the milk of lactating women were performed on women who were not breastfeeding their infants. The dose levels estimated for breastfed infants exposed to methamphetamine via milk were comparable to the dose levels calculated for breastfed infants of women taking amphetamines for medicinal use. Despite the comparable dose levels, it is not clear that a lack of adverse effects among infants exposed to amphetamines used as medicine should predict a lack of effect of methamphetamine exposure via milk in nursing infants.

10 | CONCLUSION

The purpose of this review was to summarize studies on potential developmental toxicity of amphetamines used either for medicinal purposes or abuse. Experimental animal studies of medicinal amphetamines demonstrated toxicity, including structural malformations, only when given at supratherapeutic dose levels that generally caused maternal toxicity. Behavioral studies in animals with prenatal exposure to ADHD medications showed weak if any effects. Behavioral studies in animals that examined effects of prenatal methamphetamine exposures showed conflicting results, but suggested the potential for adverse behavioral effects, especially with respect to decrements in spatial memory.

There is a large-scale population-based study on the use of amphetamines for medicinal purposes which found no increased risk of malformations after adjusting for potential confounders. Other studies on the medicinal use of amphetamines did not indicate an increased risk for structural malformations. There are three studies reporting an increased risk estimate for gastroschisis associated with medicinal or abused amphetamines, although the 95% confidence interval did not always exclude the null and each of the studies combined amphetamine exposures with exposures to other ADHD medications or to other drugs of abuse. Other studies on amphetamine or methamphetamine abuse did not indicate an increased risk for structural malformations. Prescription use of amphetamines including methamphetamine has not been associated consistently with fetal growth impairment, preterm delivery, or hypertensive disorders of pregnancy. Associations have been noted for these complications in abusers of amphetamines, but risk estimates have been unstable or of low magnitude, which might have been associated with residual confounding. Adjusting for poverty, nutrition, maternal mental health and other health problems, and use of other legal and illegal drugs remains a challenge in most studies.

No studies of neurodevelopmental effects on offspring were located for women who used amphetamines for medicinal purposes. Studies have been conducted only on the offspring of women abusing methamphetamines. These studies have documented a range of adverse effects on structural brain development and performance on tests of cognition and executive function. None of these studies adequately adjusted for one or more other factors common to women who abuse methamphetamine such as alcohol abuse, other illicit drug use, poverty, malnutrition, domestic violence, history of childhood abuse, and parent or caregiver neurobiological (psychiatric) disorders. These confounding factors suggest that the neurodevelopmental data on methamphetamine cannot be used to assess the risk of prenatal exposures to medicinally used amphetamines.

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CONFLICTS OF INTEREST

Dr A. R. S. has been a consultant for Teva, which manufactures Adderall. The other authors have no known conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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