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Gender Differences in the Outcome of Offspring Prenatally Exposed to Drugs of Abuse

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Despite great efforts to warn pregnant women that drugs of abuse impact development of the embryo and the fetus, the use of legal and illegal drugs by childbearing women is still a major public health concern. In parallel with well-established teratogenic effects elicited by some drugs of abuse, epidemiological studies show that certain psychoactive substances do not induce birth defects but lead to subtle neurobehavioral alterations in the offspring that manifest as early as during infancy. Although gender differences in offspring susceptibility have not been fully investigated, a number of longitudinal studies indicate that male and female progeny exposed *in utero* to drugs of abuse show different vulnerabilities to deleterious effects of these substances in cognitive, executive, and behavioral domains. Here, we briefly review the existing literature focusing on gender differences in the neurobehavioral consequences of maternal exposure to drugs of abuse. Overall, the data strongly indicate that male exposed progeny are more susceptible than female to dysfunctions in cognitive processing and emotional regulation. However, insights into the mechanisms determining this natural phenomenon are not currently available. Our analysis prompts future investigations to implement clinical studies including the influence of gender/sex as a biological variable in the outcome of offspring prenatally exposed to drugs of abuse.

Keywords: development, drugs of abuse, gender, neuropsychiatric, prenatal, sex, vulnerability

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INTRODUCTION

As a rule, drugs should not be used during pregnancy unless prescribed, because many can be toxic to the placenta or the developing fetus. Yet, the use of drugs, including prescription or non-prescription drugs, medicinal herbs, and licit (tobacco and alcohol) or illicit drugs, during pregnancy keeps increasing (SAMHSA, 2011). Indeed, objective measurements of xenobiotics in meconium, amniotic fluid, and cord blood indicate widespread fetal exposure to such agents during their intrauterine life (for an excellent review see Barr et al., 2007). Such exposure may induce developmental adaptations that can be interpreted as derangements from normal development, which not only interfere with the immediate viability of the fetus but may also result in the individual's adverse health outcome in the short and long term (Hales and Barker, 2001; Barker, 2007). Hence, the "developmental origin of health and disease" hypothesis (Barker, 2007) stems from epidemiological studies showing that malnutrition, exposure to xenobiotics (e.g., environmental chemicals and prescription, legal, and illegal drugs), infective diseases, or stress during specific periods of development might increase the risk of disorders later in life. This hypothesis also stresses the importance of investigating the mechanisms of fetal exposure to xenobiotics and further in general to adverse intrauterine and perinatal factors.

In this minireview, we will provide an up-to-date analysis of the evidence for a sex differential in the susceptibility to the consequences of maternal drug use on neurocognitive and behavioral development of the offspring. Research has pointed to gender differences in these sequelae, since exposed males often appear more vulnerable than exposed females. Insights into the neurobiological mechanisms underlying the sex bias observed in certain neurobehavioral outcomes remain unidentified. At this stage, we could only make inferences from animal studies, although they do not allow for a precise understanding of the underpinnings, especially in the context of sex differences. In particular, many factors might moderate the reported sex dichotomy, including individual (e.g., species, strain, age) and experimental (e.g., design, drug, dosage, route, regimen) variables, and objective endpoints (e.g., behavioral paradigm, experimental technique). Here, we attempt to integrate the gender difference results across drugs used by pregnant women. Such integration could be useful for physicians and healthcare providers when caring for a pregnant substance abusing woman. Interspecies extrapolations will be carefully avoided to ensure sound conclusions. The authors refer to excellent preclinical studies' reviews (Bruin et al., 2010; Schneider et al., 2011; Ross et al., 2015; Gkioka et al., 2016; Comasco et al., 2018; Scheyer et al., 2019).

SUBSTANCE USE IN WOMEN

The historical gap in substance use prevalence between men and women has gradually narrowed in the past decade, particularly among adolescents (Keyes et al., 2008; Seedat et al., 2009; Steingrimsson et al., 2012; EMCDDA, 2019). While women still exhibit lower rates of drug use disorder than men, prevalence rates indicate that the number of female drug abusers is on the rise. A recent snapshot of the European drug use situation shows that women account for one-quarter of the general population with drug issues and around one-fifth of all first-time drug abuse treatment seekers (EMCDDA, 2019). Gender differences are clear in the pattern of use at each stage of the addiction cycle. Women typically begin to use substances later in life (Greenfield et al., 2010; Keyes et al., 2010), misuse prescription drugs (e.g., opioids) (McHugh et al., 2013), and their rate of consumption increases more rapidly than that of men (Greenfield et al., 2010; Keyes et al., 2010). Women also exhibit higher prevalence rates of comorbidity with other psychiatric disorders as well as of relapse (Wilcox and Yates, 1993; Conway et al., 2006; Back et al., 2011; Khan et al., 2013).

DRUG USE DURING PREGNANCY AND BREASTFEEDING: EFFECTS ON MALE AND FEMALE OFFSPRING

The consumption of drugs in childbearing women has been progressively increasing. Women abusing recreational drugs before pregnancy tend to continue the use even during gestation (Forray, 2016), and this use is not limited to illegal drugs but includes prescription and over-the-counter drugs. Approximately 60% of pregnant women take prescription drugs and about 13% of them use herbal supplements. Furthermore, the infographics based on the National Survey on Drug Use and Health (SAMHSA, 2018) show that 5.4% of pregnant women have used illicit drugs in the past 30 days, while 9.9 and 11.6% reported past-month alcohol or cigarette smoking use, respectively. To complicate this issue, many women take drugs when they are not aware of being pregnant.

Regardless of their legal status, all drugs cross and/or alter the placental barrier, reach the fetus, and affect infant development. Additionally, multiple drugs also pass into mother's breast milk, thus resulting in prolonged drug exposure of the newborn. According to the United States Centers for Disease Control and Prevention, almost 3% of newborns have birth defects because of genetic, environmental, or other unknown causes (Parker et al., 2010). Among environmental factors, drug use is the major cause leading to birth defects ranging from fetal growth reductions to medical complications such as preterm birth and infections. Furthermore, the progeny prenatally exposed to drugs of abuse develop neurobehavioral phenotypes that manifest during infancy and persist to adolescence and young adulthood. Research on the effects of prenatal alcohol, tobacco, opioids, stimulants, and cannabis indicates an association between fetal exposure to these substances and deficits in cognitive and behavioral domains. However, in humans, the role of fetal sex on functional consequences of prenatal exposure to drugs of abuse remains grossly understudied. Here we present data on illicit psychostimulants, opioids, cannabis, nicotine, and alcohol in an attempt to provide a clear picture of neurobehavioral outcomes in male and female progeny. When gender differences have not been examined, our interpretation is limited to the overall outcome.

Effects of *in utero* Exposure to Psychostimulants

Psychostimulants, including cocaine and methamphetamine, are the illicit drugs most commonly used by childbearing women, though no recent estimate of their consumption during pregnancy is known. Despite their well-described neurotoxic effects on central nervous system (CNS) development, only very few studies have addressed the negative neurobehavioral sequalae on human offspring, particularly when gender is included as an additional biological variable (**Table 1** and **Figure 1**).

Longitudinal studies of long-term consequences of cocaine use during pregnancy on the offspring focusing on emotional regulation, behavior, and cognition suggest that female gender is a protective factor (Singer et al., 2004; Dennis et al., 2006; Accornero et al., 2007; Bennett et al., 2008; Ackerman et al., 2010; Bridgett and Mayes, 2011). Male progeny exhibit stronger impairment in inhibitory response, whereas females exhibit only mild alterations that disappear with age (Carmody et al., 2011). Accordingly, male offspring exhibit greater emotion regulation problems and externalizing symptoms (e.g., aggressive and risky behaviors); lower intellectual capabilities; and deficits in attention, short-term memory, and problem solving compared

TABLE 1 | Detailed information on the studies covered in this minireview examining gender as a variable.

Author year	Substance	Type of study	Experimental groups	Neuro developmental outcome	Prenatal polysubstance exposure	Socioeconomic status	Age	Performed tasks	Gender results
Prenatal psychostimulant exposure									
Lu et al., 2009	Meth amphetamine	Cross-sectional study	Methamphetamine exposed vs alcohol exposed vs control	Cognitive abilities	Yes (methamphetamine, alcohol)	Matched for socioeconomic status	7–15 year	Wechsler Intelligence Scale for Children, 4th Edition (WISC-4), California Verbal Learning Test for Children (CVLT-C)	Impaired verbal learning capacities in methamphetamine and alcohol exposed
Diaz et al., 2014	Meth amphetamine	Longitudinal study	Exposed vs control	Cognitive abilities	Yes (methamphetamine, alcohol, cannabis, tobacco)	Matched for socioeconomic status	7.5 year	Conners' Parent Rating Scale–Revised: Short Form (CPRS-R:S)	Significantly higher cognitive problems scores in exposed children
Piper et al., 2011	Meth amphetamine	Cross-sectional study	Methamphetamine and polysubstance exposed vs Unexposed	Cognitive Abilities	Yes (methamphetamine, alcohol, tobacco, cannabis)	Matched for socioeconomic status	7–9 year	Wechsler Abbreviated Scale of Intelligence, Conners' Continuous Performance Test II, Behavioral Rating Inventory of Executive Function, the CMS Family Pictures and Dot Location tests, the Spatial Span test from WISC-IV-Integrated, and a recently developed spatial learning and memory measure (Memory Island)	Exposed children show deficit in executive functions (e.g., behavioral regulation and metacognition) and spatial memory
Kiblawi et al., 2013	Meth amphetamine	Longitudinal	Exposed vs unexposed	ADHD risk	Yes (methamphetamine, alcohol, cannabis, tobacco)	Controlled for low socioeconomic status	5 year	Conners' Kiddie Continuous Performance Test (K-CPT)	KCPT scores suggest higher ADHD risk for exposed children
LaGasse et al., 2012	Meth amphetamine	Longitudinal study	Exposed vs unexposed	ADHD risk	Yes (methadone, alcohol and tobacco, cannabis)	Adjusted for low socioeconomic status	3–5 year	Child Behavior Checklist	Higher prevalence of ADHD symptoms in exposed males than girls
LaGasse et al., 2012	Meth amphetamine	Longitudinal study	Exposed vs unexposed	Behavioral problems	Yes (methadone, alcohol and tobacco, cannabis)	Adjusted for low socioeconomic status	3–5 year	Child Behavior Checklist	More externalizing problems and aggressive behavior in exposed males than girls
Bennett et al., 2008	Cocaine	Longitudinal study	Exposed vs unexposed	Cognitive abilities	Yes (cocaine, alcohol, tobacco, cannabis)	Measured as environmental risk	4, 6, 9 year	Stanford-Binet IV intelligence test	Lower composite IQ score (abstract/visual and verbal reasoning, short-term memory) in exposed boys but not girls

(Continued)

TABLE 1 | Continued

Author year	Substance	Type of study	Experimental groups	Neuro developmental outcome	Prenatal polysubstance exposure	Socioeconomic status	Age	Performed tasks	Gender results
Dennis et al., 2006	Cocaine	Longitudinal study	Exposed vs unexposed	Cognitive abilities	Yes (cocaine, alcohol, tobacco, cannabis)	Measured as environmental risk	5 year	The impossible pulley task	More difficulties in problem solving and altered reactivity/ regulating behavior in exposed males than females
Singer et al., 2004	Cocaine	Longitudinal study	Exposed vs non-exposed	Cognitive abilities	Yes (cocaine, alcohol, tobacco, cannabis)	Measured as caregiving environmental risk	0–4 year	Wechsler Preschool and Primary Scales of Intelligence-Revised	Mild but significant difficulties in cognitive abilities (visual-spatial and arithmetic skills) in exposed males
Mayes et al., 2003	Cocaine	Longitudinal study	Exposed vs non-drug and non-cocaine-exposed	Cognitive abilities	Yes (cocaine, alcohol, tobacco, cannabis)	Measured as environmental risk	0–3 year	Bayley Scales of Infant Development (BSID-II)	Lower BSID-II mental performance in cocaine exposed children compared to both non-drug and non-cocaine-exposed children
Accornero et al., 2007	Cocaine	Longitudinal study	Exposed vs unexposed	Deficit in attention and inhibition response	Yes	Matched for socioeconomic status	5–7 year	Continuous performance tests (CPTs)	Deficits in attention processing in exposed offspring
Karmel and Gardner, 1996	Cocaine	Longitudinal study	Exposed vs unexposed	Attention and arousal	Yes (cocaine, alcohol, tobacco)	ND	0–1 year	Visual looking preferences	Arousal-modulated attention deficit in exposed male and female infants
Bennett et al., 2007	Cocaine	Longitudinal study	Exposed vs unexposed	Neurobehavioral problems	Yes (cocaine, alcohol, tobacco, cannabis)	Adjusted for low socioeconomic status	10 year	Youth Risk Behavior Survey	Highest scores for aggression, substance use, high-risk behavior in exposed males
Nordstrom Bailey et al., 2005	Cocaine	Longitudinal study	Exposed vs unexposed	Neurobehavioral problems (aggressive behavior)	Yes (cocaine, alcohol)	Controlled for socioeconomic status	6–7 year	Achenbach Teacher Report Form (TRF)	Delinquent behavior and clinically significant externalizing behavior scores in exposed boys
Sood et al., 2005	Cocaine	Historical prospective study	Alcohol exposed vs cocaine and/or alcohol exposed	Neurobehavioral problems	Yes (cocaine, alcohol)	Controlled for socioeconomic status	6–7 year	Caregiver reported Achenbach Child Behavior Checklist (CBCL)	Higher aggressive (in females) and delinquent behaviors (in males) scores in exposed offspring
Bendersky et al., 2006	Cocaine	Longitudinal study	Exposed vs unexposed	Neurobehavioral problems	Yes (cocaine, alcohol, tobacco, cannabis)	Measured as environmental risk	5 year	ACHENBACHChild Behavior Checklist (CBCL), LRRH Reinisch Revision, Teacher Rating of Aggression (TRA)	Aggressive behavior in exposed male offspring

(Continued)

TABLE 1 | Continued

Author year	Substance	Type of study	Experimental groups	Neuro developmental outcome	Prenatal polysubstance exposure	Socioeconomic status	Age	Performed tasks	Gender results
Prenatal opioid exposure									
Nygaard et al., 2015	Heroin	Longitudinal study	Heroin exposed vs polysubstance exposed	Cognitive abilities	Yes (heroin, benzodiazepines, alcohol)	Controlled for low socioeconomic status	1–3 year	Bayley Scales II (Mental Development Index, MDI)	Significantly and stably lower levels of cognitive functioning in male progeny
Nygaard et al., 2015	Heroin	Longitudinal study	Heroin exposed vs polysubstance exposed	Cognitive abilities	Yes (heroin, benzodiazepines, alcohol)	Controlled for low socioeconomic status	4 year	McCarthy Scales of Children's Abilities	Significantly and stably lower levels of cognitive functioning in male progeny
Nygaard et al., 2015	Heroin	Longitudinal study	Heroin exposed vs polysubstance exposed	Cognitive abilities	Yes (heroin, benzodiazepines, alcohol)	Controlled for low socioeconomic status	8 year	The Wechsler Intelligence Scale for Children—Revised	Significantly lower cognitive scores in both exposed males and females
Nygaard et al., 2017	Heroin	Longitudinal study	Heroin exposed vs polysubstance exposed	Cognitive abilities	Yes (heroin, tobacco, benzodiazepines, alcohol, psychopharmaca)	Matched for socioeconomic status	17–21 year	Wechsler Abbreviated Scale of Intelligence (WASI), The Rey Complex Figure Test (RCFT), The California Verbal Learning Test – 2nd Ed (CVLT-II), Wechsler Adult Intelligence Scale 3rd Ed(WAIS-III)	Significantly worse cognitive performances in male and female exposed offspring compared to controls
Suffet and Brotman, 1984	Methadone	Longitudinal study	Exposed males vs exposed females	Cognitive abilities	ND	ND	0–2 year	Bayley Scales (Mental Development Index, MDI)	Significantly lower cognitive scores in both male and female exposed offspring
Ornoy et al., 2001	Heroin	Longitudinal study	Exposed vs unexposed	Inattention/ hyperactivity phenotype or risk for ADHD	Yes (heroin, methadone, benzodiazepines and other psychoactive drugs)	Compared for socioeconomic status	8 year (5–12 year)	The Conners and Achenbach questionnaires and the Pollack Taper test	Highest rate of ADHD in both heroin exposed boys and girls
Prenatal tobacco exposure									
Moe and Slinning, 2001	Tobacco	Longitudinal study	Exposed vs unexposed	Cognitive abilities	Yes (tobacco, opioids, alcohol, cannabis, psychostimulants, and more)	Compared for socioeconomic status	1–3 year	Bayley Scales II (Mental Development Index, MDI)	Lower Mental Developmental Scores in exposed male infants
Kotimaa et al., 2003	Tobacco	Longitudinal study	Exposed vs control	Hyperactivity phenotype and ADHD risk	Yes (tobacco and alcohol)	Adjusted for socioeconomic status	8 year	Children's Behavior Questionnaire (Rutter B2)	Hyperactivity in males and females prenatally exposed to nicotine
Willoughby et al., 2007	Tobacco	Epidemiological Study	Exposed vs control	Attention, reactivity, irritability	Yes (tobacco, alcohol)	Adjusted for socioeconomic status	0–1 year	Infant Behavior Record (IBR)	Significantly lower cognitive performances in exposed males

(Continued)

TABLE 1 | Continued

Author year	Substance	Type of study	Experimental groups	Neuro developmental outcome	Prenatal polysubstance exposure	Socioeconomic status	Age	Performed tasks	Gender results
Cornelius et al., 2007	Tobacco	Longitudinal study	Exposed vs unexposed offspring from teenager mothers	Inattention/ hyperactivity phenotype	Yes (tobacco, cannabis, alcohol)	Controlled for socioeconomic status	6 year	Child Behavior Checklist, RouthActivity Scale, and the SNAP	Increased activity and attention problems in both male and female exposedoffspring
Gatzke-Kopp and Beauchaine, 2007	Tobacco	Longitudinal study	Exposed vs unexposed	Neurobehavioral problems, ADHD and cognitive abilities	Yes (tobacco, alcohol, cannabis, amphetamines, heroin)	Controlled for socioeconomic status	7–15 year	Child Behavior Checklist (CBCL; Achenbach, 1991), Child Symptom Inventory (CSI)	Exposed offspring shows more severe ADHD symptoms and cognitive behavioral problems
Langley et al., 2007	Tobacco	Cross-sectional study	Exposed with ADHD vs unexposed with ADHD	ADHD diagnosis	ND	Measured as environmental risk	7–8 year	Clinical diagnosis	Maternal smoking in pregnancy and high environmental risk, independently influence the clinical presentation of the ADHDphenotype without sex-vulnerability
Hutchinson et al., 2010	Tobacco	Longitudinal study	Exposed vs unexposed	ADHD risk and neurobehavioral problems	ND	Confounding factor	3 year	SDQs	Higher risk for conduct and hyperactivity–inattention problems in males whose mothers persistently smoked throughout pregnancy
Wakschlag and Hans, 2002	Tobacco	Longitudinal study	Exposed vs unexposed	Neurobehavioral problems (conduct disorder)	Yes (tobacco, alcohol, opioids, cannabis)	Controlled for socioeconomic status	10 year	The Diagnostic Interview for Children and Adolescents (DICA)	Exposed boys, but not girls, are significantly more likely to develop conduct disorder symptoms
Fergusson et al., 1998	Tobacco	Longitudinal study	Exposed vs unexposed	Neurobehavioral problems (conduct disorder)	Yes (tobacco, alcohol, illicit drugs)	Adjusted for socioeconomic status	16–18 year	Composite International Diagnostic Interview and the Self-Report Delinquency Inventory	More severe conduct disorders symptoms in male adolescents than in females prenatally exposed to tobacco
Prenatal alcohol exposure									
Richardson et al., 2002	Alcohol	Longitudinal study	Exposed vs control	Cognitive abilities	Yes (alcohol, cannabis, tobacco, cocaine)	Controlled for low socioeconomic status	10 year	Wisconsin Card Sorting Test, Wide Range Assessment of Memory and Learning (WRAML), Trail Making	Significantly lower cognitive scores (learning and memory) in both male and female exposed offspring
Howell et al., 2006	Alcohol	Longitudinal study	Exposed vs control	Cognitive abilities	Yes (alcohol, cannabis, tobacco, cocaine)	Controlled for low socioeconomic status	15 year	Wechsler Intelligence Scale for Children (WISC-III), Wechsler Individual Achievement Test (WIAT)	Significantly lower IQ score and mathematical abilities in both male and female exposed offspring

(Continued)

TABLE 1 | Continued

Author year	Substance	Type of study	Experimental groups	Neuro developmental outcome	Prenatal polysubstance exposure	Socioeconomic status	Age	Performed tasks	Gender results
Kelly et al., 2009	Alcohol	Longitudinal study	Exposed vs control	Cognitive abilities	Yes (alcohol, tobacco)	Adjusted for low socioeconomic status	3 year	British Ability Scale (BAS), Bracken School Readiness Assessment (BSRA)	Significantly lower cognitive scores in males born to heavy-drinking mothers compared to exposed females
Willford et al., 2004	Alcohol	Longitudinal study	Exposed vs control	Cognitive abilities	Yes (alcohol, cannabis, tobacco, cocaine)	Controlled for low socioeconomic status	14 year	Children's Memory Scale	Deficits in learning, short-term and long-term memory, specifically in the verbal domain, in both exposed males and females
Coles et al., 2002	Alcohol	Longitudinal study	Exposed vs control	Inattention/ hyperactivity phenotype	Yes (alcohol, cannabis, tobacco)	Controlled for low socioeconomic status	15 year	Continuous performance task (CPT)	Deficits in sustained attention, processing in the visual and auditory modality in exposed progeny
Herman et al., 2008	Alcohol	Cross-sectional study	FASD offspring with ADHD vs FASD offspring	ADHD diagnosis	ND	Controlled for low socioeconomic status	6–16 year	ADHD diagnosis	Higher prevalence of ADHD diagnosis in exposed males than females
Kelly et al., 2009	Alcohol	Longitudinal study	Exposed vs control	Behavior problems (hyperactivity, conduct, peer problems)	Yes (alcohol, tobacco)	Adjusted for low socioeconomic status	3 year	Parent-report version of the Strengths and Difficulties Questionnaire (SDQ)	Exposed males were more likely to have clinically relevant high total difficulties, hyperactivity, conduct and peer problems compared to girls
Prenatal cannabis Exposure									
Noland et al., 2005	Cannabis	Longitudinal study	Exposed vs control	Cognitive abilities	Yes (cannabis, tobacco, alcohol, cocaine)	Controlled for low socioeconomic status	4 year	Picture deletion task (PDT), continuous performance task (CPT), Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R)	Higher omission error rates in exposed offspring
El Marroun et al., 2011	Cannabis	Longitudinal study	Exposed vs control	Attention problems	Yes (cannabis, tobacco, alcohol)	ND	1–2 year	Child Behavior Checklist	Prenatal cannabis is associated with attention problems specifically in exposed girls
Richardson et al., 2002	Cannabis	Longitudinal study	Exposed vs control	Cognitive abilities, attention and impulsivity	Yes (alcohol, cannabis, tobacco, cocaine)	Controlled for low socioeconomic status	10 year	Continuous performance test	Deficit in memory and learning, together with higher impulsivity score in both males and females

(Continued)

TABLE 1 | Continued

Author year	Substance	Type of study	Experimental groups	Neuro developmental outcome	Prenatal polysubstance exposure	Socioeconomic status	Age	Performed tasks	Gender results
El Marroun et al., 2011	Cannabis	Longitudinal study	Exposed vs control	Behavioral problems (aggressive behavior)	Yes (cannabis, tobacco, alcohol)	ND	1–2 year	Child Behavior Checklist	Externalizing problems (aggressive behavior) in girls during early childhood
Day et al., 2011	Cannabis	Longitudinal study	Exposed vs control	Behavioral problems (delinquent behavior)	Yes (cannabis, tobacco, alcohol)	Matched	14 year	Self-Report Delinquency scale and Child Behavior Checklist	Delinquent behavior in exposed offspring of heavy marijuana users

A thorough description of each study is presented with designed study type, experimental groups enrolled, outcomes, occurrence of poly-drug use, socioeconomic status, age at assessment, type of task used, and gender results. Gender effect is displayed as pink and blue for female and male progeny, respectively. Gender differences not observed are white.

to female offspring (Bennett et al., 2002, 2007, 2008; Delaney-Black et al., 2004; Nordstrom Bailey et al., 2005; Sood et al., 2005; Bendersky et al., 2006; Dennis et al., 2006; Carmody et al., 2011). In contrast, no gender dichotomy was found in the occurrence of attention deficit/hyperactivity disorder (ADHD) phenotypes from infancy to preadolescence (Karmel and Gardner, 1996; Mayes, 1996; Mayes et al., 1998, 2003; Accornero et al., 2007).

With regard to methamphetamine, the most frequent outcomes reported in newborns occur during the first year of life and include motor dysfunctions (e.g., disorganized behaviors with poor quality of movement), which tend to disappear with development in boys (LaGasse et al., 2012; Shah et al., 2012; Zabaneh et al., 2012; Kiblawi et al., 2014), whereas they persist throughout adolescence in girls (Eriksson and Zetterström, 1994; Cernerud et al., 1996). In contrast, other neurobehavioral problems (e.g., anxious/depressive phenotypes, emotional problems) appear during late infancy and childhood and do not exhibit sex bias (LaGasse et al., 2012). Similarly, impairments in cognitive skills occur equally in both female and male offspring (Lu et al., 2009; Piper et al., 2011; Diaz et al., 2014). However, deficits in inhibitory control and ADHD-like symptoms are prevalent in boys (LaGasse et al., 2012; Kiblawi et al., 2013).

Effects of Prenatal Exposure to Opioids

Regardless of the efforts aimed at discouraging opioid use, prevalence rates show an increasing trend in pregnant women (Haight et al., 2018). However, gender was not considered in most of the human studies on the effects of heroin, methadone, and other prescription opioids.

Children born to mothers who use opioids during gestation suffer from the so-called neonatal opioid withdrawal syndrome (NOWS) (Gomez-Pomar and Finnegan, 2018), characterized by several signs and symptoms (e.g., tremors, sleep problems, hyperactive reflexes, vomiting, dehydration, and respiratory problems), which are more severe in boys than in girls (Jansson et al., 2007, 2010). Maternal consumption of methadone—the gold standard for opioid maintenance therapy—is associated with poorer cognitive performance and lower IQ scores in exposed males when compared to females during infancy, an age-dependent effect (Suffet and Brotman, 1984; Nygaard et al., 2015). However, no gender difference is found in symptoms related to ADHD and aggressive behavior up to preadolescence (Ornoy et al., 2001).

Effects of Maternal Tobacco

Nicotine and its related tobacco products are the most studied substances in relation to long-term neurobehavioral outcomes in offspring exposed to tobacco during pregnancy. Despite the limitations due to several environmental confounding factors, a high degree of consistency exists for the association of maternal smoking and cognitive and behavioral problems (for an exhaustive review, see England et al., 2017). From these studies emerge a male bias toward diverse behavioral and cognitive domains, depending on age: at 6–8 months, males appear more vulnerable to deficits in cognitive and executive functions (e.g., inattention) and in motor functions and to alterations in

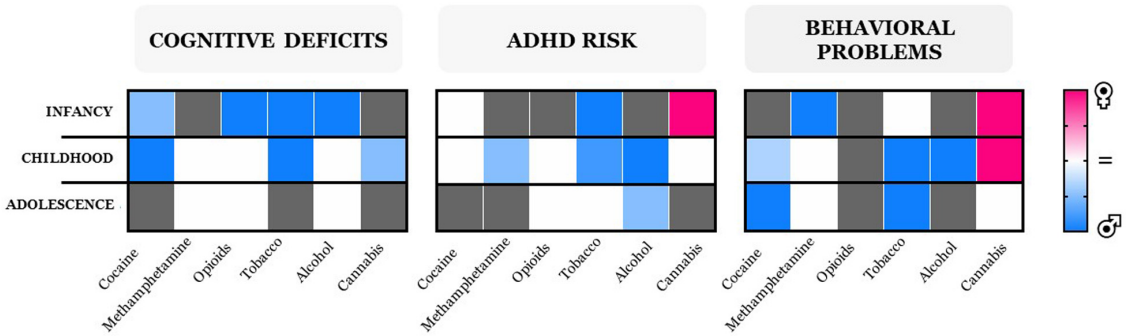

FIGURE 1 | Heatmaps of neurobehavioral outcomes collectively identified as cognitive deficits (including executive function), ADHD risk, and behavioral problems, with missing information on gender differences shown in gray. Outcome intensities are displayed as colors ranging from pink (female) to blue (male) shown in the key. Gender differences were not observed in executive functions during childhood in offspring prenatally exposed to cocaine in one study only (Accornero et al., 2007); therefore, the heatmap displays blue as a result of the larger number of consistent studies reporting that boys are more susceptible to exhibit deficits in cognitive abilities when compared to girls (see text and also **Table 1**).

reactivity (Moe and Slinning, 2001; Wakschlag and Hans, 2002; Willoughby et al., 2007). From infancy through childhood, boys appear at risk for ADHD (Kotimaa et al., 2003; Cornelius et al., 2007; Willoughby et al., 2007; Agrawal et al., 2010; Hutchinson et al., 2010); however, only during infancy do they display less positive mood (Pickett et al., 2008) than females; during childhood and adolescence, males present more externalizing and disruptive behaviors (e.g., conduct disorders, antisocial behavior) than females (Wakschlag et al., 1997; Fergusson et al., 1998; Hutchinson et al., 2010). Conversely, parental tobacco exposure is associated with nicotine dependence and high consumption of tobacco only in adolescent girls (Rydell et al., 2012). Although the risk of developing ADHD symptoms in nicotine-exposed progeny is high during adolescence, no gender differences were found (Gatzke-Kopp and Beauchaine, 2007; Agrawal et al., 2010; Sourander et al., 2019).

Effects of Maternal Alcohol

Despite the widely described dose-dependent teratogenic effect of alcohol (Kodituwakku, 2007; Ornoy and Ergaz, 2010), approximately 10% of women aged between 15 and 44 years consume alcohol during pregnancy, with 3% exhibiting a binge-drinking pattern (SAMHSA, 2011). Irrespective of the amount and pattern of consumption, a wealth of clinical evidence describes that prenatal alcohol exposure markedly impairs cognitive, behavioral, and motor functions of offspring (Mattson et al., 1998; Coles et al., 2002; Richardson et al., 2002; Willford et al., 2004; Riley and McGee, 2005; Howell et al., 2006). Maternal moderate to heavy drinking produces a group of pathological conditions termed fetal alcohol spectrum disorder (FASD). Epidemiological studies report sexual dichotomy in FASD, with prevalence rates and severity being higher in male than in female patients (May et al., 2007; Astley, 2010; Thanh et al., 2014; but see May et al., 2014; Fox et al., 2015). A sex bias is also described for other psychopathological traits, such as elevated rates of ADHD in 6- to 16-year-old boys but not girls (Coles et al., 2002; Herman et al., 2008). Boys also exhibit altered responses to stress, measured as larger changes in cortisol levels induced by stress-related cues (Haley et al., 2006). In contrast, neuroimaging studies do not reveal sex differences in long-term abnormalities of brain morphology because the reduction in both size and volume of frontal, temporal, cingulate, and striatal regions of offspring prenatally exposed to alcohol did not differ between genders (Eckstrand et al., 2012; Treit et al., 2013; De Guio et al., 2014). These findings suggest that such psychopathological traits cannot be attributed to these structural changes.

Effects of *in utero* Cannabis Exposure

In line with the data on general population, the rates of cannabis use among pregnant women have markedly increased, with prevalence rates reaching 75% between 2002 and 2016 (Brown et al., 2017). Despite this alarming scenario, a few studies have assessed the long-term neurobehavioral repercussions of maternal cannabis use on the offspring, though gender differences were not consistently examined: the *Ottawa Prenatal Prospective Study* (OPPS), the *Maternal Health Practices and Child Development Project* (MHPCDP), the *Generation R* study, and *Adolescent Brain Cognitive Development* (ABCD) study. The OPPS study included gender as a confounding factor, and it described a number of long-lasting neurobehavioral alterations, ranging from heightened tremors and startle responsiveness to deficits in executive function (e.g., attention, cognitive flexibility, problem solving, impulse control) (Fried and Makin, 1987; Fried and Smith, 2001). Similarly, gender was not examined when assessing performance in memory, verbal, and perceptual processes as well as the first clinical signs of impulsivity at childhood (Smith et al., 2006). However, when the same authors subsequently included the gender factor on clinical signs that persisted at young adulthood, such as deficits in executive function tasks that require impulse control, they found no gender differences (Smith et al., 2004). In the MHPCD study, the authors seldom included "gender" in their analysis. However, they reported (1) significant sleep disturbances and deficits in mental development as well as in short-term memory and verbal reasoning at both 9 months and 3 years of age; (2) deficits in attention and memory, increased anxiety/depressive

symptoms, impulsivity, hyperactivity, and aggression at 6 and 14 years of age (Richardson et al., 1989, 2002; Dahl et al., 1995; Leech et al., 2006; Day et al., 2011). Gender at 10 years of age did not affect cognitive deficits (Richardson et al., 2002). In contrast, the Generation R study showed that girls but not boys at 18 months of age exhibited increased scores on an aggressive behavior scale that persisted through childhood (El Marroun et al., 2011). Notably, this sex bias disappears during adolescence. Also, during infancy girls appear to be at risk for the development of ADHD, a susceptibility that is age dependent (**Table 1** and **Figure 1**). Remarkably, although from Generation R and ABCD studies maternal cannabis use has been associated to proneness to psychosis in middle to late childhood, significantly earlier than the typical onset of first psychotic episode (Bolhuis et al., 2018; Fine et al., 2019; Paul et al., 2019), again gender was not considered. Importantly, an independent investigation showed that prenatal marijuana exposure has an equally negative effect on sustained attention of the offspring from childhood to adolescence (Noland et al., 2005).

CONCLUSION

The literature here examined reveals gender differences in immediate and long-term negative consequences of maternal drug use on both cognition and behavior. When gender was included as a variable, irrespective of the drug used, male progeny appear more vulnerable to cognitive deficits and at risk of ADHD from infancy through childhood (**Table 1** and **Figure 1**). Notably, these gender differences tend to disappear with age. However, we cannot depict a clear picture for internalizing problems, drug use, and motor function deficits due to the paucity of data. Regarding the problems in the behavioral domain (i.e., externalizing problems), the current scenario is clearer: girls exposed *in utero* to cannabis are more vulnerable than boys up until adolescence, but this conclusion cannot be extended to other drugs. Remarkably, this is in contrast to what is often reported in rodent studies (Fernandez-Ruiz et al., 1998; Hurd et al., 2019; Scheyer et al., 2019; de Salas-Quiroga et al., 2020), where female sex often acts as a protective factor. Nevertheless, the advantage of animal studies is to dissect the effects of genetic, biological, and/or environmental risk factors. The establishment of a biological causality between prenatal drug exposure and repercussions on the progeny from animal investigations is pivotal. These mechanistic insights along with the observations reported in human studies may help in developing therapeutic interventions, on a gender-specific basis, which would ultimately result in more effective treatment outcome.

The longitudinal studies examined have often considered different factors that might have contributed to gender differences, including socioeconomic status, lifestyle indicators, stressful life events, social support (or lack thereof), and psychiatric comorbidity. In this regard, an additional degree of complexity arises from the evidence that single drug use is virtually non-existent. At this stage, we cannot certainly resolve this issue in human studies, as it deserves as much attention as neuroimaging and omics analyses to reveal neurobiological underpinnings of drug-exposed phenotypes. Of similar importance is the need to study the association between the perturbations of *in utero*–placental exchange and adverse mental health outcome later in life. Indeed, increasing evidence points to the role of the placenta in fetal programming, which is altered in response to prenatal insults and contributes to psychopathology (Burton et al., 2010; Khalife et al., 2012; Roescher et al., 2014; Park et al., 2018; Kratimenos and Penn, 2019). Notably, the placenta influences in a sex-dependent manner the outcome for offspring who were exposed to perinatal malnutrition and stressors (Walsh et al., 2019). However, research into whether the gender bias results from sex differences in placental structure and functions or its genes, proteins, and steroids is surprisingly lacking. Hence, future research should aim at disentangling how sex impacts neurobiology from the transfer of maternal drug concentrations across the placenta to the effect on placental gene transcription or expression of discrete transporters (e.g., ATP-binding cassette carriers) in the cord. In fact, to date, such investigations have been performed only to relate maternal drug use and placental perturbations to fetal growth and other morphological abnormalities (Janssen et al., 2015).

Substance (ab)use screening protocols, including questionnaires and urine toxicology testing, should be established worldwide as routine to identify pregnant women using drugs. Public health interventions regarding the awareness of the harm associated with maternal drug use, and special programs to enter treatment and/or increase spontaneous quit rates, should be implemented (Jantzen et al., 1998; Forray, 2016 and references therein; Patrick et al., 2017). Progress on tailored, safe, and acceptable pharmacotherapies to restore proper neurodevelopmental trajectories of the progeny should be incentivized. Additional preventative outreach programs should be implemented to raise community awareness and support and to provide access to treatment for the children who are prenatally exposed to drugs. Finally, future investigations should be implemented to include the influence of sex as a biological variable (for guidelines please refer to (Clayton, 2018; Mannon et al., 2020) in the outcome of offspring prenatally exposed to drugs of abuse.

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All authors participated in the conceptualization, design, and preparation of the manuscript.

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