

Methodological Issues in Assessing the Impact of Prenatal Drug Exposure

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ABSTRACT: Prenatal drug exposure is a common public health concern that can result in perinatal complications, birth defects, and developmental disorders. The growing literature regarding the effects of prenatal exposure to specific drugs such as tobacco, alcohol, cocaine, and heroin is often conflicting and constantly changing. This review discusses several reasons why the effects of prenatal drug exposure are so difficult to determine, including variations in dose, timing, duration of exposure, polydrug use, unreliable measures of drug exposure, latent or “sleeper” effects, genetic factors, and socioenvironmental influences. In addition to providing research guidelines, this review also aims to help clinicians and policy makers to identify the strengths and weaknesses in studies investigating the effects of prenatal drug exposure. This knowledge may be used to make better informed decisions regarding the appropriate treatment for pregnant, drug-dependent women and their children.

KEYWORDS: prenatal drug exposure, child development, drug addiction, pregnancy

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Introduction

Substance abuse during pregnancy is a major public health concern that affects both the mother and the growing infant.¹ According to the 2013 U.S. National Survey on Drug Use and Health, 5.4% of all pregnant women reported current illicit drug use, 9.4% reported alcohol use, and 15.4% reported cigarette use.² However, the actual number of children who have been exposed to drugs in utero may be even higher since pregnant women often underreport the substance use.³ Prenatal drug exposure can have severe negative effects on fetal development that may persist into adulthood. In utero exposure to alcohol can lead to fetal alcohol spectrum disorder (FASD), which is the leading, nonhereditary cause of intellectual disability in the Western world.⁴ FASD is characterized by growth retardation, facial dysmorphism, and intellectual disability associated with central nervous system (CNS) dysfunction. Besides alcohol, other drugs have also been reported to have negative effects on the newborn. Prenatal opioid exposure leads to neonatal abstinence syndrome (NAS) in 50%–80% of all opioid-exposed infants, which is characterized by gastrointestinal, respiratory, autonomic, and CNS disturbances.⁵ Tobacco smoking during pregnancy has been suggested to produce significant long-term developmental and behavioral teratogenic effects.⁶ The effects of

prenatal cocaine exposure are less clear, with some studies reporting negative effects on cognitive development,⁷ while others claim that these findings are correlated with other factors, such as polydrug use and the quality of the child's environment.⁸

The purpose of this review article is to address various methodological issues related to the assessment of prenatal drug exposure effects. While numerous reviews have reported the effects of prenatal drug exposure on children's development, few have described the field from a methodological perspective. In this review, information was compiled by various searches in PubMed, MEDLINE, Google Scholar, from personal archives, and reference lists from papers. In addition to providing a checklist for good research design, this article also aims to help clinicians and policy makers to identify shortcomings in studies investigating the effects of prenatal drug exposure, thereby helping them to better weigh their results. The first part of this review will discuss how the properties of a drug, as well as dose, timing, and duration of exposure can influence fetal development. The second part will deal with issues related to measuring drug exposure and the assessment of developmental outcomes. In the third and final part, the potential confounding influences of polydrug exposure and socioenvironmental influences are addressed.



Drug Properties, Dose, Timing, and Duration

It is well known that neurotransmitters play a critical role in various neurodevelopmental processes, including neuronal proliferation, migration, differentiation, and apoptosis.⁹ Since nearly all psychoactive drugs enter the circulation of the developing fetus, maternal intake of these drugs has the potential to disrupt fetal brain architecture and chemistry.¹⁰ The degree to which these drugs influence fetal development depends on several factors, including the physicochemical properties of the drug, dose, timing, and duration of exposure. Most drugs enter the bloodstream of the embryo and fetus by passive diffusion. The rate and extent of transfer depend on several characteristics such as lipid solubility, polarity, and molecular weight of the drug.¹¹ Drugs that have a low molecular weight, high lipid solubility, and that are predominantly unionized cross the human placenta more easily than the drugs with a large molecular mass, low lipid solubility, and extensive ionization.^{11,12} For instance, ethanol has a molecular weight of 46 g/mol and may therefore cross the placenta more easily than caffeine, which has a molecular mass of 194 g/mol. Drugs that are easily transferred into the bloodstream of the fetus may have a greater effect on development than drugs that do not easily cross the placenta, although developmental outcomes will also depend on the toxicity and pharmacologic properties of the drug.¹³

Besides, the type of drug and the concentration of drug in the fetal circulation are also of importance. Effects will be seen only when fetal concentrations reach a certain minimum threshold.¹⁴ For instance, FASD generally occurs only when women consume more than 80 g of alcohol a day during pregnancy.¹⁵ Conversely, subtle neurobehavioral effects, such as hyperactivity, attention problems, and poor motor coordination, may occur even at low levels of alcohol consumption. Consequently, it is still debated whether there exists a “safe” level of consumption.¹⁴ The potential teratogenic effect of a drug may also depend on the developmental stage of the embryo or fetus at the time of exposure.¹⁶ Most morphological abnormalities are caused by exposure early in pregnancy, growth is most commonly affected by the late exposure, while CNS deficits can occur throughout gestation.¹⁷ As a result, drug exposure during the first weeks of pregnancy may not result in similar developmental outcomes as drug exposure during the second or third trimester or exposure throughout the entire pregnancy.

Timing and dosage effects have important implications for the study design. To be able to detect exposure effects, participants need to have been exposed to drug concentrations above the “minimum” threshold for that specific drug. In addition, they need to have been exposed at a time during pregnancy where exposure has an effect on the outcome measures used in the study. For instance, when studying FASD-related facial dysmorphism, it is important to include participants who have been prenatally exposed to alcohol during the first trimester of pregnancy and who have been exposed to

relatively high levels of alcohol, since morphological anomalies are caused by relatively high levels of exposure early in pregnancy.¹⁷ However, when studying subtle neurobehavioral effects of prenatal alcohol exposure, one might also include participants who have been exposed to small amounts of alcohol or who have been exposed in late pregnancy only since CNS deficits can occur even at low levels of exposure and by exposure throughout the entire pregnancy.¹⁷

Legal Versus Illegal Drugs

While much focus and research has been devoted to the effects of illegal drug use during pregnancy, some legal drugs, such as alcohol or nicotine, can be equally or even more harmful to the developing fetus.¹⁸ Moreover, the majority of pregnant women who use illegal substances during pregnancy also use legal drugs.¹⁹ The use of legal drugs during pregnancy may therefore affect more children than illegal drugs and should be strongly discouraged. To illustrate this, Slotkin¹⁸ conducted an animal study comparing the effects of fetal nicotine with cocaine exposure. Both nicotine and cocaine are vasoconstrictors that can evoke acute episodes of fetal hypoxia–ischemia, causing insufficient blood flow to cells and organs, which can cause cell damage. When these drugs were injected into pregnant rats, nicotine caused more cell damage than cocaine, as indicated by higher postnatal elevations in CNS ornithine decarboxylase activity. Contrary to nicotine exposure, cocaine exposure did not lead to irrevocable cell loss, and the observed effects were short-lived, allowing for recovery to occur in between doses, whereas the effects of nicotine persisted.¹⁸ Based on these results, it was concluded that the effects of prenatal cocaine exposure were less severe than those of prenatal nicotine exposure. However, since cocaine use is more strongly associated with other hazardous behaviors, such as self-injury, developmental outcomes may still be more negative for children prenatally exposed to cocaine than for children exposed to nicotine. Nonetheless, this study suggests that some legal drugs may be as harmful as or even more harmful to the developing fetus than illegal drugs. It is therefore crucial that studies report both illegal and legal drug exposure as this may critically affect developmental outcome.

Measuring Prenatal Drug Exposure

In order to investigate the effects of prenatal drug exposure, it is essential to have good exposure measurements. The most common methods to assess prenatal drug exposure are maternal self-report and urine toxicology screens, but infant meconium and infant hair analysis are also used.²⁰ Maternal urine toxicology screens can detect several drugs, including cocaine, amphetamine, marijuana, barbiturates, and opiates. However, it can only detect recent drug use and cannot measure quantity or frequency of drug use.^{12,20} Alcohol can also be detected by urine toxicology screens but only within 24 hours of ingestion.²⁰ Because of the short detection time, urine toxicology screens often result in an underreporting of drug exposure.



Infant meconium and hair analyses, which can detect long-term exposure and give information about the quantity and frequency of drug use, are also therefore commonly used. Still, these methods also have several limitations. Meconium is only available during the first few days after birth, and infants are not always born with enough hair to take hair samples. In addition, both the formation of meconium and hair growth take place after the first trimester of pregnancy, which may result in underreporting of drug exposure that occurred in the first trimester.^{20,21} Maternal self-report, if correct, provides the best measure of drug exposure since it not only gives information about the type of drug exposure but also the amount, frequency, and duration.²¹ However, pregnant women often fail to report drug use for fear of losing their baby to child protective services.²² Also, even when mothers are willing to disclose such information, maternal reports of the type and extent of drug use are often inaccurate.²¹ Clearly, all measures of prenatal drug exposure have weaknesses that can result in underreporting. Studies investigating the effects of prenatal drug exposure should therefore use a combination of maternal self-report and laboratory methods.

Acute Versus Chronic Drug Effects

While it is critical to have accurate measures of drug exposure, it is equally important to have carefully selected outcome measures. Generally, the effects of prenatal drug exposure on the fetus can be divided into two groups: (i) acute effects that are short term and commonly diminish over time and (ii) chronic effects that can manifest themselves months or even years after birth.¹² A widely reported outcome of prenatal drug exposure is physical dependency of the fetus that can result in NAS (as defined earlier). NAS is characterized by tremors, irritability, excessive crying, and diarrhea and results from the dysregulation of the autonomic nervous system.²³ NAS has been most commonly associated with prenatal opioid exposure, but other drugs, especially those acting as CNS depressants such as barbiturates and alcohol, have also been found to cause fetal behavior consistent with withdrawal.²⁴ Since the effects of prenatal drug exposure on the developing nervous system are extremely complex, it is difficult to separate the acute effects, such as NAS, from the chronic effects of drug exposure. These chronic effects can be present immediately after birth, such as physical CNS anomalies found in alcohol-exposed infants,²⁵ but this is not always the case. Some effects that do not manifest themselves immediately as prenatal drug exposure can cause subtle anomalies that do not become evident until later in development when more complex cognitive functions begin to emerge.²⁶ Such delayed effects, named latent or “sleeper” effects, may occur even in the absence of neonatal complications. For instance, Fisher et al.²⁷ investigated 1,073 youths with prenatal cocaine exposure and found evidence for a delayed effect of prenatal exposure on executive function. Specifically, prenatal exposure only predicted executive function difficulties during adolescence but not during

childhood. To fully map the effects of prenatal drug exposure, it is therefore essential to follow up drug-exposed children long into adolescence.

Global Versus Specific Effects

When assessing the effects of prenatal drug exposure, it is also important to consider that drugs may influence development on a global level and on a more specific subtle level. For instance, it has been found that prenatal alcohol exposure is related to decreased IQ score and increased behavior problems at school age.²⁸ Conversely, prenatal cocaine exposure has not been found to lead to general developmental delays at school age but to more specific deficits in sustained attention and behavioral self-regulation.²⁹ Traditional, standardized tests of cognitive functioning, such as the Bayley Scales of Infant Development (BSID), Wechsler Preschool and Primary Scale of Intelligence, and Wechsler Intelligence Scale for Children, are commonly used to assess the effects of prenatal drug exposure on children’s general development.^{30–32} These tests require children to pay attention, remember instructions (except BSID), and to use a combination of cognitive and fine-motor skills, and are therefore, sensitive to a wide range of brain functions.¹⁴ On the other hand, this also makes it difficult to identify which specific function is impaired when test scores are low. Global tests should therefore preferably be supplemented with more specific tests of cognitive functioning. For instance, prenatal methadone exposure has been associated with poorer smooth pursuit eye movements and visual selective attention, which can affect children’s performance on standardized tests.^{33,34} Similarly, prenatal cocaine exposure has been found to be related to deficits in sustained attention.²⁹ Attention problems affect children’s performance on standardized intelligence tests.³⁵ Consequently, studies may erroneously conclude that prenatal cocaine exposure leads to deficits in general IQ if separate attention measures are not used.

Psychophysiological Measures

Besides focused behavioral tests, psychophysiological measures can also be useful when studying the effects of prenatal drug exposure. Psychophysiological measures can identify which specific neurobiological substrates might be affected, they can measure unique processes that other measures cannot measure, and they are often more sensitive compared to behavioral measures.³⁶ Electroencephalogram (EEG) studies on the effects of prenatal alcohol exposure on infant sleep brain activity found that alcohol-exposed newborns have elevated EEG powers during sleep compared to controls.^{37,38} These EEG abnormalities were present even in the absence of FASD and related to subsequent mental and motor development.³⁸ Although the exact mechanisms behind this association are still unclear, these EEG results can be used to identify at-risk infants at an early stage, which may lead to early intervention and improved developmental outcomes. Advances in the field of magnetic resonance imaging (MRI) have also improved our under-



standing of the effects of prenatal drug exposure on development. Toro et al.³⁹ investigated cortical thickness in prenatally tobacco-exposed adolescents as measured by volumetric MRI. Results revealed exposed adolescents had thinner orbitofrontal (OFC), middle frontal, and parahippocampal cortices compared to nonexposed adolescents. Interestingly, this difference was only found in females, suggesting that females might be more vulnerable to the effects of prenatal tobacco exposure than males. Since the OFC plays a significant role in social interaction and behavior, these results may explain why adolescents with prenatal tobacco exposure have a higher prevalence of social and behavior problems.⁴⁰ To conclude, focused tests and psychophysiological measures can help identify specific areas affected by prenatal drug exposure, which is important for the intervention. In addition, they can provide valuable information about the underlying mechanisms by which prenatal drug exposure can alter brain functioning. Accordingly, these tests should be administered in addition to global, standardized assessments of cognitive, behavioral, and motor functioning when studying the effects of prenatal drug exposure.

Polydrug Use

One of the major challenges in the field of behavioral teratology is polydrug use. A large multicenter study with over 10,000 pregnant women participating found that polydrug use was very common among women who used cocaine or opiates during pregnancy.⁴¹ Specifically, they found that 93% of all women who used cocaine or opiates during pregnancy also used alcohol, tobacco, and/or marijuana. Polydrug use makes it difficult to study the effects of a specific drug on child development, since the effects of other drugs may influence study outcome. The importance of controlling the polydrug use has been illustrated in a study by Richardson and Day.⁴² In this study, children of frequent cocaine users had lower birth weights compared to nonusers. However, when alcohol and tobacco use during pregnancy were controlled, the difference in birth weight disappeared between the two groups. Similarly, it was found that cocaine use during pregnancy was not associated with prematurity, Apgar scores, or head circumference after controlling for alcohol, tobacco, marijuana, and other illicit drug use. If this study had not controlled polydrug use, it would have appeared that prenatal cocaine use had a direct negative effect on birth outcome. But in fact, these differences in birth outcome reflect the impact of polydrug use rather than cocaine exposure.

Socioenvironmental and Genetic Risk Factors

Another major research challenge when studying the effects of prenatal drug exposure relates to socioenvironmental and genetic factors. It is widely acknowledged that children prenatally exposed to drugs are also at an increased risk of experiencing instability in their social environment. Drug-dependent parents are more than two-fold likely to physically and/or sexually abuse their children.^{43,44} Since childhood physical and mental abuse are negatively associated with cognitive develop-

ment, this is important to consider. While the exact mechanisms between child abuse and poor cognitive functioning are still not fully understood, brain trauma from physical injury, understimulation, and an unstable learning environment may be linking factors.⁴⁵ Drug use is also highly associated with psychopathology, specifically mood and anxiety disorders. In a review by Jane-Llopis and Matytsina,⁴⁶ it was found that prevalence rates for comorbidity between drug use disorders and mental disorders ranges across studies from 8% up to 70%, varying by type and severity of drug dependence. This association has been found for most drugs but is specifically strong for women abusing sedatives, tranquilizers, or opioids.⁴⁷ Compared to nondrug users, drug-dependent women also experience higher levels of parent-related stress,^{48,49} are less responsive during mother–infant interaction,⁵⁰ and are more punitive toward their children.⁵¹ Maternal psychopathology and stress can have a negative impact on children's development. Specifically, parents who experience stress, anxiety, and/or depression often have less positive interactions with their infant, which increases the infant's need for self-regulation, limiting exploration, learning, and social interactions with others.⁵² These infants may in addition stop seeking help from others when they experience repetitive interactional failures, which can hinder their cognitive and social development.⁵²

Besides socioenvironmental risk factors, genes may also play an important role. For instance, it has been found that children of drug-dependent mothers are at an increased risk of developing attention deficit/hyperactivity disorder (ADHD) even when they are not raised at home by their biological mother but adopted away.⁵³ Although this could be a direct exposure effect, this increased rate of ADHD in drug-exposed children correlated with maternal ADHD, which suggests that the high rates of ADHD found among children of drug-dependent women may have a genetic component. Clearly, children of drug-abusing parents face multiple risks that need to be taken into consideration when investigating the effects of prenatal drug exposure. Although animal studies can control environmental and genetic risk factors by random assignment, human studies cannot randomly assign offspring to specific prenatal or postnatal conditions. This makes it specifically difficult to assess whether prenatal exposure has a direct causal effect on child development. Consequently, a range of potential risk factors known to be related to child outcome, including maternal psychopathology, low education, unemployment, isolation, single parenthood, poor maternal–child interaction, low income, poor prenatal care, and perinatal medical risk factors need to be considered. These risk factors can not only be used as control variables but also to test risk and resilience models investigating which factors increase or decrease the effects of prenatal drug exposure.¹⁴

Controlling for Covariates

Polydrug use, genetic, and environmental factors make it difficult to identify the specific direct effects of prenatal drug



exposure on children's outcome. If these factors are not accounted for, developmental effects may be erroneously attributed to prenatal drug exposure (Type I error). One way to deal with this problem is to control for these factors in the analysis. On the other hand, adjusting for too many covariates can cause a decrease in statistical power, which increases the probability that true prenatal drug effects are not detected (Type II error).⁵⁴ As a result, control variables need to be screened carefully and included only if they are related to child outcome.¹⁴

In addition, it is necessary to differentiate between confounders and mediators. Take, for instance, the variable birth weight. Cocaine, heroin, tobacco, and alcohol use during pregnancy have been associated with a decrease in birth weight,^{55,56} which is negatively associated with cognitive development, general intelligence, motor skills, and learning abilities.⁵⁷⁻⁵⁹ One possibility is that low birth weight in children of drug-dependent women is a result of lifestyle-associated factors, such as poor maternal nutrition, maternal infections, and late and infrequent antenatal care attendance.⁵⁶ In this case, the variable birth weight is a confounder in the relationship between prenatal drug exposure and poor developmental outcome. Another possibility is that prenatal drug exposure directly influences birth weight. Prenatal opioid exposure has been suggested to influence fetal growth through its interaction with the opioid growth factor, a negative regulator of tissue growth.^{60,61} Prenatal opioid exposure may, therefore, have a direct negative effect on fetal growth and birth weight. In this case, the variable birth weight mediates the effects of prenatal drug exposure on children's outcome through a direct causal pathway. Controlling for birth weight could consequently obscure direct teratogenic drug effects. Thus, before including variables such as birth weight in an analysis, it should be carefully considered whether to conceptualize them as confounders or mediators.

Conclusion

Prenatal exposure to legal and illegal psychoactive drugs is a major preventable health problem that contributes to various health risks. Several issues were raised in this article that should be addressed when studying the effects of prenatal drug exposure. First, there are large differences in the amount, frequency, and type of exposure among children. Since prenatal drug effects will depend on these factors, the specific physicochemical properties of the drug under study need to be well understood and taken into account. Second, since exposure to legal drugs, such as tobacco and alcohol, can be just or even more harmful than exposure to illegal drugs, it is important to report both legal and illegal drug exposure. Illegal drug use during pregnancy is almost always combined with legal drug use. If legal drug use is not accounted for, negative outcomes may be erroneously attributed to the illegal drug, while in fact it is an effect of polydrug use. Third, since the extent to which drugs influence fetal development depends on the physicochemical properties of the drug, as well as dose, timing and duration of exposure, it is vital to use sensitive and reliable measures of drug exposure. To

achieve this, it is preferable to use a combination of maternal self-report and laboratory measurement. Fourth, the negative effects of prenatal drug exposure may not become apparent until later in development. It is, therefore, essential to follow up drug-exposed children long into adolescence. Fifth, besides, global tests of developmental functioning, sensitive focused behavioral, and psychophysiological measures also need to be used. In some cases, prenatal drug exposure is only associated with subtle problems in development, which global screening tests may fail to detect. Even if these subtle problems are not apparent in everyday functioning, they can emerge under challenging or stressful circumstances or when children get older and are thus important to assess.⁶² Sixth, polydrug use is a common issue that needs to be addressed carefully. If not, the effects of one drug can be wrongfully attributed to another, which can have serious consequences when pregnant women are advised about the dangers of specific drugs. Seventh and finally, maternal drug use frequently occurs in the context of a range of socioenvironmental risk factors, including maternal psychopathology, poverty, and low parental education. As such, prenatal drug exposure is just one of many risk factors in these children's lives. Although older studies have commonly attributed poor developmental outcome to either direct teratogenic effects or environmental influences, it is now commonly accepted that the developmental outcomes of drug-exposed children are determined by a combination of biological, psychosocial, and environmental factors.⁶³ Consequently, both drug exposure and other risk factors should be taken into consideration and carefully controlled while studying the effects of prenatal drug exposure. In conclusion, there are many problems to overcome when investigating the effects of prenatal drug exposure on children's development. Addressing all of these problems is a daunting task at best, which requires systematic large-scale, longitudinal studies. Only then can appropriate intervention strategies be implemented and developmental problems, which unfortunately are common following prenatal drug exposure, be prevented.

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Wrote the first draft of the manuscript: CK. Contributed to the writing of the manuscript: CK. Agree with manuscript results and conclusions: CK. Jointly developed the structure and arguments for the paper: CK. Made critical revisions and approved final version: CK. The author reviewed and approved of the final manuscript.

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