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Fifty Years of Research on Prenatal Substances: Lessons Learned for the Opioid Epidemic

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Abstract

Current efforts to design research on developmental effects of prenatal opioid exposure can benefit from knowledge gained from 50 years of studies of fetal alcohol and prenatal drug exposures such as cocaine. Scientific advances in neurobiology, developmental psychopathology, infant assessments, genetics, and imaging support the principles of developmental neurotoxicology that guide research in prenatal exposures. Important to research design is accurate assessment of amount, frequency, and timing of exposure which benefits from accurate self-report and biomarkers of exposure. Identifying and control of pre- and postnatal factors that impact development are difficult and dependent on appropriate research design and selection of comparison groups and measurement of confounding, mediating, and moderating variables. Polysubstance exposure has increased due to the number of prescribed and nonprescribed substances used by pregnant women and varying combinations of drugs may have differential effects on the outcome. Multiple experimental and clinical assessments of infant behavior have been developed but predicting outcome before 18–24 months of age remains difficult. With some exceptions, prenatal substance exposure effect sizes have been small, and cognitive and behavioral effects tend to be specific rather than global. Studies require large sample sizes, adequate retention, and support for social services in at-risk samples. The ethical and legal contexts and stigma associated with drug/alcohol use disorder should be considered in order to prevent harm to families in research programs. Recognition of the pervasive use of addictive substances in this nation should lead to broad scientific efforts to understand how substances affect child outcomes and to initiate prevention and intervention where needed.

Keywords

Drugs; Alcohol; Opioid crisis; Research design; Prenatal substance exposure

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Introduction

At a national meeting on supporting infants bom with prenatal opioid exposure, a group of foster parents, pediatricians, obstetricians, addictionologists, and federal funders discussed the numerous social, mental health, educational, and treatment needs of opioid affected families. Two colleagues immediately turned to each other and said “Déjà vu all over again.” They had been struck with how much of the discussion was reminiscent of those heard 30 years earlier during the cocaine epidemic. Today, understanding the developmental outcomes of prenatally opioid-exposed (POE) children has become a pressing national concern. The number of women of child-bearing age reporting misuse of prescription opioids or of heroin reached epidemic proportions over the past decade (Haight, Ko, Tong, Bohm, & Callaghan, 2018), as has the impact of infants born with neonatal opioid withdrawal syndrome (NOWS) (Strahan, Guy, Bohm, Frey, & Ko, 2019). Understanding the parallels and differences between the two epidemics, in the context of decades of research on prenatal exposure to other substances including alcohol, can inform the design of national developmental studies now planned to assess sequelae of fetal opioid exposure.

Historical Context for Behavioral Teratology

A confluence of several scientific advances informed the design of earlier research studies on fetal alcohol and drug exposures and continue to be relevant to the investigation during the opioid epidemic. The development of the field of behavioral teratology, now called developmental neurotoxicology, is one (Vorhees, 1986). Numerous studies on prenatal alcohol exposure conducted worldwide after the “discovery” of fetal alcohol syndrome (FAS) (Jones & Smith, 1973) in the 1970s reported that embryotoxicity could manifest in a range of effects on functions not detectable as frank malformations. These early studies documented, and recent studies continue to define, a range of behavioral effects that occur at lower thresholds of substance exposure than those associated with physical anomalies (Coles, Kable, Taddeo, & Strickland, 2018; Streissguth, Sampson, Barr, Clarren, & Martin, 1986). Similarly, studies of environmental contaminants, such as lead, demonstrated that even low levels of exposure can be related to negative health, learning, and behavioral sequelae (Min et al., 2009; Needleman & Landrigan, 1981; Needleman & Leviton, 1979). The application of randomized clinical trials (RCTs) to infancy interventions (Singer, 2001) and burgeoning knowledge of the processes of fetal brain development also provided contexts for current study designs related to POE (Nelson, 1999). Other important influences include the growing recognition of the major roles of socioeconomic and caregiving factors in child development (Sameroff & Chandler, 1975), the refinement of infant assessments, both clinical and experimental (Bayley, 1969; Sameroff & Chandler, 1975; Singer & Zeskind, 2001), and recognition that specific disabilities, such as autism, hyperactivity attention-deficit disorder, and deficits in learning and behavior, can occur in the context of average or above-average global IQ. More recently, the application of imaging techniques (Coles & Li, 2011; Dow-Edwards et al., 2006) and the contribution of genetics (Dodge, Jacobson, & Jacobson, 2014; Jacobson, Jacobson, Sokol, Martier, & Chiodo, 1996) and epigenetics have increased the understanding of the association of prenatal substance exposures to life span development. These scientific advances have elucidated the principles of developmental neurotoxicology in relationship to fetal exposures to alcohol and drugs.

In addition to the recognition of the functional consequences of exposure independent of malformation, developmental neurotoxicology recognizes the reciprocal roles of genetics and environment, the importance of developmental stage at the time of insult, the threshold of the dose required to produce effects, the development of dose-response relationships between exposure and outcomes, and the potential for compensatory mechanisms (Vorhees, 1986). Also, important is the period of development during which outcomes are measured. In accordance with these constructs, this paper addresses methodologic considerations critical to accurate appraisal of the impact of POE on child outcomes.

Considerations for Accurate Measurement of the Independent Variable by Maternal Report

Ethical and Social Context

Although it was common to address the problem of maternal substance use and child outcome by comparing users and nonusers, years of research have demonstrated that understanding sequelae of prenatal opioid exposure requires accurate measurement of the amount, timing, and frequency of exposure. This can be a difficult task in the investigation of illegal or socially undesirable substances, such as opiates, for a number of reasons. Because illegal drugs are not packaged in standard dosages and are likely to be adulterated with other substances, investigators need to be knowledgeable about local nomenclature, distribution, costs, types of packaging, and adulterants of drugs in their geographic region. In addition, there can be changes over time in access to an illicit drug and its potency. For example, there has been accelerated use of medical and recreational marijuana, including among pregnant women, over the past decade following legalization in many states. Over the same time period, increasing levels of the primary psychoactive ingredient, tetrahydrocannabinol (THC), have been noted (Volkow, Han, Compton, & McCance-Katz, 2019). Similarly, prescription opioids have increased in potency over the last few decades and it is difficult to define the composition of illicit drugs like heroin.

Even when considering exposure to legal substances, pregnant women are likely to deny or to minimize their use of alcohol, tobacco, or any substance considered to be harmful, due to social desirability and/or fear of stigmatization (Jacobson, Chiodo, Sokol, & Jacobson, 2002; Volkow, 2020). In some states, admission of use of illegal substances may result in mandated reports for child abuse (Room, 2005) to courts or government agencies and even lead to incarceration, a frequent and problematic occurrence during the cocaine epidemic (Paltrow, Cohen, & Carey, 2000; Rubenstein, 1991). Research studies that can be separated from the mandate to report drug use during pregnancy, e.g., by recruiting women after identification of exposure, have a higher likelihood of obtaining honest responses from women and thus obtaining reliable estimates of exposure. Truthfulness is also affected by the context in which the interview occurs, including privacy, assurance of confidentiality, perception of interviewer judgment, and identification and rapport with the interviewer (Day & Robles, 1989).

Quantity, Frequency, and Gestational Timing of Exposure

It is particularly difficult to obtain information about first trimester use without self-disclosure although this is a particularly important period of development. If the measurement of substance use does not include self-report, some drug effects that may occur only in the first trimester can be missed (Coles, 1994). Most studies to date have demonstrated that women tend to decrease their use of substances over their pregnancy (Coles et al., 2018; Moore et al., 2010; Palmsten et al., 2018; Singer et al., 2002) so that relying on quantitative data only from the second and third trimesters may obscure the relationship of substances with outcomes. For example, thalidomide's major teratogenic sequela, phocomelia, is evident only when exposure occurs in the brief first trimester window of post-conception days 23–34 (Vargesson, 2015). Likewise, in a study of middle class methylenedioxymethamphetamine (MDMA) users in the UK, the majority of women ceased all use of the drug after the first trimester, so without accurate first trimester disclosure, MDMA relationships to developmental outcomes would have been missed (Moore et al., 2010; Singer et al., 2016). Averaging out drug use over all the trimesters of the pregnancy may also obscure effects that are trimester specific (Coles, 1994).

Assessments that rely only on average quantity and frequency of consumption (e.g., "How many drinks do you have on the days that you drink?" and "How many days a week do you drink?") may miss associations that relate to specific patterns of use, such as binge drinking, and thus may yield serious underestimates of exposure at a given time in gestation. Considering maximum and minimum levels of consumption contributed an additional 45% and 17%, respectively, to overall total use estimates in one study of marijuana use during pregnancy (Day & Robles, 1989). Employing longitudinal trajectory modeling across all trimesters of pregnancy detected different risk patterns for adverse infant outcomes in one study of prenatal alcohol exposure (Bandoli et al., 2019). Likewise, different patterns of substance use have been associated with varying birth outcomes (Shankaran et al., 2004).

Best Practices to Enhance Accurate Maternal Recall

Other factors to be considered in interviewing pregnant women regarding substance use include the participants' ability to remember the exact details regarding exposure and their understanding of the researcher's questions. When truthful, contemporaneous reporting of the quantity of alcohol ingested provides the most valid measure of exposure (Jacobson et al., 2002). The timeline follow-back (TLFB) interview (Sobell & Sobell, 1992) has been found to facilitate more accurate recall of substance use over pregnancy for postpartum assessment by anchoring memory of day-to-day substance use to the time pregnancy was diagnosed, as well as to the time the subject knew she was pregnant and to the time conception occurred. Asking subjects to describe use in their own terms led Day and Robles (1989) to develop questions that asked subjects to report on quantity first and then frequency to reduce complexity and subject frustration, a method that they found showed high reliability with blood alcohol measures.

Considerations for Accurate Measurement of the Independent Variable with Biomarkers

The use of biomarkers to detect substance exposure such as hair, urine, blood, and meconium (Bakhireva et al., 2018; Bearer et al., 1999; Gutierrez et al., 2015; Ostrea Jr, Brady, Gause, Raymundo, & Stevens, 1992) has enhanced exposure identification. However, biomarkers which rely on metabolic evidence in body tissue, by their very nature, primarily identify recent use. When recruitment is done around birth, first trimester use, perhaps the most vulnerable period, cannot be reliably assessed using biomarkers. Meconium, obtained postnatally, develops only in the second trimester and the windows for detection in urine, hair, and blood comprise only days to weeks of exposure. Since no measure is perfectly accurate, combining biomarkers with maternal self-report provides the strongest likelihood of detection and the greatest accuracy of exposure. Some examples are useful in understanding how different measures can refine the classification of exposure. In one study of cocaine users, comparing self-report and quantification of meconium revealed differences in detection of use and also changed the classification of some women from lighter to heavier users (Arendt, Singer, Minnes, & Salvator, 1999). In another study, the detection of opiate and marijuana use was significantly enhanced by adding urine screens to interview data (Garg et al., 2016).

Identification and Control of Confounding Factors Associated with Substance Use in Pregnancy

Importance of Sample Selection and Use of Appropriate Comparison/Contrast Groups

In the investigation of many exposures, separating specific teratogenic sequelae from both pre- and postnatal environmental factors that also impact development has proved to be difficult due to the multiple variables influencing child outcomes that are often associated with maternal substance use. This problem points up the importance of research design in accurate identification of the impact of specific substances. Accomplishing identification of specific exposure effects against this background requires both appropriate research design, including care in the selection of sample population and comparison groups, and longitudinal models, as well as accurate assessment of potentially confounding variables. For example, studies of cocaine-exposed infants in the USA were primarily carried out in samples of unmarried, urban, African-American women of low-socioeconomic status, lower IQ, and low levels of education, with a high incidence of depressive symptoms, inadequate prenatal care, and exposure to violence (Bendersky, Alessandri, Gilbert, & Lewis, 1996; Coles, Platzman, Smith, James, & Falek, 1992; Richardson, Hamel, Goldschmidt, & Day, 1996). Although these studies employed appropriate contrast groups, social and psychological factors were often confounded with drug use and related to child outcomes (Bandoli et al., 2016; Salisbury et al., 2007; Singer et al., 2002). As a result, to date, virtually, nothing is known about the use of cocaine by women of middle or higher socioeconomic (SES) during pregnancy and its effects on off-spring. Thus, the selection of samples of convenience to investigate the impact of cocaine led to exposure being significantly confounded with the effects of disadvantage and racial inequity and may have

resulted in inaccurate conclusions, in the short term, at least (Coles, 1993). In other studies, appropriate contrast groups that are matched on potentially confounding variables are not always used, with the result that effects can be attributed to the exposure which are actually related to some covariate. The need to control for multiple potential confounders is illustrated by one longitudinal study of fetal alcohol effects, in which 150 covariates were evaluated (Streissguth et al., 1986).

Importance of Confounding by Socioeconomic Status, Mental Health, and Child Placement

To the extent that identification of substance use during pregnancy is affected by social class, understanding of child outcomes can be biased. Identification of women and screening for substance use may be biased towards disadvantaged women (Matera, Warren, Moomjy, Fink, & Fox, 1990). This has been observed in research on alcohol exposure. Higher rates of FAS have been diagnosed in disadvantaged minority groups (May, Hymbaugh, Aase, & Samet, 1983; Sokol et al., 1986) and were less likely to be diagnosed in upper-middle-class White infants in a study of chronic alcoholics (Bingol et al., 1987). Coles and Kable (1998) have noted that in some research studies, race and SES were confounded and the FAS diagnosis itself may be biased because cognitive outcomes, one of the diagnostic criteria, are confounded with SES.

To address such bias, many studies of cocaine-exposed infants enrolled comparison women from the same screened or comparable risk population (Bendersky et al., 1996; Coles et al., 1992; Singer et al., 2002). Despite such efforts, groups still differed on multiple parameters that affect infant outcomes, including education, SES, marital status, and comorbidity. In one study (Singer et al., 2008), a significant percentage of cocaine-exposed infants were fostered or adopted early in infancy into non-kinship homes where caregivers were of middle or upper-class SES, with better environments as measured by the HOME scale (Caldwell & Bradley, 1984), less lead exposure and had caregivers of higher IQ and education than their birth families or the comparison group that was recruited. The enriched foster/adoptive care environments were associated with a lower likelihood of a diagnosis of intellectual disability at age 9 in the exposed group (Singer et al., 2008). In another study, positive gains in developmental outcome also occurred in out of home placements but only in those that were non-kinship care as opposed to kinship care (Brown, Bakeman, Coles, Platzman, & Lynch, 2004). In contrast, although women identified with opioid use disorders are primarily White and span all SES classes, epidemiologic data indicate that they also are frequently diagnosed with psychological disorders such as posttraumatic stress disorder, phobia, and personality disorders and exhibit physical disabilities and pain (Kerridge et al., 2015), all factors that researchers must account for in their infant studies. As with cocaine-exposed infants, many children with POE are placed in foster, adoptive, or kinship care, making follow-up and measurement of the changing caregiving environment a challenge (Larson et al., 2019).

Polydrug Exposure to Multiple Substances and Psychotropic Medications

Frequency of Co-exposures and Potential Interactive Effects

Subsequent to the cocaine epidemic, research on prenatal exposures has become much more sensitive to the problem of polysubstance use. By the 1980s, it was already well recognized that cocaine- or heroin-exposed infants were impacted by a “cocktail” of drugs during the prenatal period. In fact, often cocaine-using pregnant women were found to be using more alcohol, marijuana, and tobacco than comparison women who were recruited specifically to control for those other substances (Bendersky et al., 1996; Coles et al., 1992; Singer et al., 2002). Studies of opioid users during the late 1970s and early 1980s (Hans & Jeremy, 2001) also identified alcohol, marijuana, and tobacco use as common correlates in methadone-treated pregnant women. Since that time, there has been an increase in the use of prescription medications, both as prescribed and illicitly, during pregnancy, that include stimulants, antidepressants, benzodiazepines, gabapentin, and non-benzodiazepine hypnotics. This is also true of pregnant women already receiving an opioid prescription (Dawson et al., 2015; Hanley & Mintzes, 2014; Hwang et al., 2016). Although some medications such as selective serotonin reuptake inhibitors (SSRIs) have been extensively studied (Chambers et al., 2006; Santucci et al., 2014; Wisner et al., 2009), there is almost no information on developmental effects of other drugs such as benzodiazepines and other psychotropics on the infant (Lupattelli et al., 2019). In one study, the relative risk of neonatal opioid withdrawal syndrome (NOWS) was significantly increased in neonates exposed to both opioids and psychotropic medications compared to opioids alone (Huybrechts et al., 2017), but there are virtually no studies evaluating how these drug combinations affect developmental outcome.

Similarly, the co-abuse of benzodiazepines and opioids has been described as “substantial,” with high rates (50–70%) of benzodiazepine abuse noted in methadone and buprenorphine-maintained patients (Gelkopf, Bleich, Hayward, Bodner, & Adelson, 1999; San, Torrens, Castillo, Porta, & de la Torre, 1993). Alcohol use disorder (AUD) prevalence has been estimated to be 35–50% among patients in methadone treatment in Europe (Soyka, 2014), along with regular marijuana and benzodiazepine consumption (Backmund, Schutz, Meyer, Eichenlaub, & Soyka, 2003). In the USA, meta-analyses of clinical trials found alcohol use disorder in 38% of patients seeking opioid treatment (Hartzler, Donovan, & Huang, 2010). Alcohol use, not meeting criteria for AUD, may be even more common. Cocaine, marijuana, and tobacco use are also frequent concomitants to methadone maintenance programs (Margolin et al., 1995), with rates of cocaine abuse among patients reported to be from 58 to 75% (Ball, Corty, Bond, & Tommasello, 1988; Condelli, Fairbank, Dennis, & Rachal, 1991). In one study, marijuana was the most frequently identified drug in patients entering detoxification compared to heroin, cocaine, and amphetamines (Brooner, King, Kidorf, Schmidt Jr, & Bigelow, 1997). Finally, estimates indicate that 95% of pregnant women with opioid use disorders smoke cigarettes (Jones et al., 2013).

Polydrug Exposure and Implications for Study Design

Many of these drugs have been shown to have specific adverse effects on child cognitive, physical, and behavioral outcomes but have not been studied in interaction with each other

or with opioid exposure. Inattention to study design, through lack of recruitment of a truly comparable control group, can prevent the conclusive assessment of prenatal substance exposure relationships (Li et al., 2009). For example, in one review and meta-analysis, exposure to medication for addiction treatment was no longer related to cognitive outcome once studies with tobacco exposure were considered (Nelson et al., 2020). The authors found that an overall negative association of exposure to the cognitive outcome was associated with an imbalance in the recruitment of comparison mothers with different SES, education, and tobacco use. One approach to address the question of polydrug exposure is found in the ENRICH study that employed two contrast groups to allow comparison to the group of women enrolled in opioid maintenance therapy. Opiate-maintained women's alcohol use was carefully measured. One comparison group included women also in treatment for opioid use disorder but who had abstained from alcohol use. A second comparison group was comprised of women who abstained from alcohol and were lifetime nonusers of illicit drugs and tobacco (Bakhireva, Lowe, Gutierrez, & Stephen, 2015; Beauchamp et al., 2020).

Understanding the effects of opioid-polysubstance use on the fetus is important because their additive or synergistic effects may be different from those of opioids alone. Polydrug exposure may increase the risk to the fetus or, counterintuitively, may be a moderator of negative opioid effects dependent on the type of substance, dosage, and timing of exposure. When opioids are combined with alcohol or benzodiazepines, the reward effects of opioids are enhanced, but respiratory depression is exaggerated, and this combination of drugs has been implicated in 50–85% of heroin deaths (Huang & Lee, 2013). When stimulants are used with opioids, the sedative effects are masked, sometimes resulting in extreme heart rate variability, increased blood pressure, and heart rate effects. Some drug combinations may have unique biochemical effects on the developing fetal brain. Cocaethylene, for example, is a unique byproduct of combining cocaine and alcohol, with higher toxicity levels than cocaine alone, and has been shown to predict poor fetal growth in some studies (Singer, Arendt, Song, Warshawsky, & Kliegman, 1994).

Another consideration to be addressed through study design is the potential contribution of substance exposure through breastfeeding. In contrast to women who use cocaine in the postpartum period, women in treatment for opiate dependence are encouraged to breastfeed in order to foster an attachment relationship (Larson et al., 2019). Thus, women in opioid treatment who are also using alcohol, marijuana, tobacco, or other substances are transferring these substances to the infant through breast milk which may have negative effects on developmental outcomes (Bertrand, Hanan, Honerkamp-Smith, Best, & Chambers, 2018).

Analytical and Sample Size Considerations

Despite the difficulty of assessing the unique and synergistic effects of polysubstance exposure that is pervasive in prenatally opioid-exposed infants, multimodal assessment of maternal use of substances during pregnancy and long-term follow-up will be important in ultimately understanding the impact of opiate exposure on the developing fetus and child. Establishing the true relationship between POE and outcomes involves a priori recognition of potentially confounding variables based, as noted above, on their known relationship to

outcomes. Strategies of statistical control, matching, stratification, or exclusion can help in this regard. However, critical to evaluating covariates is determining whether they should be considered as confounding, mediating, or moderating variables (Baron & Kenny, 1986; Jacobson and Jacobson, 2005). Determining whether a covariate is a confounder, a mediator, or a moderator is dependent on the empirical literature, the theoretical models guiding the study, and the statistical relationships among variables (Baron & Kenny, 1986). A covariate can be both a mediator and a moderator. If variables such as birth parameters that are mediators are treated as confounders, drug effects may be missed. For example, prenatal cocaine, alcohol, and tobacco exposure have been linked to lower gestational age, smaller head circumference, and low birth weight, all of which are known to correlate independently with developmental risk. Controlling for these factors could then result in type II error, when in fact many studies have found that early growth parameters mediated drug or alcohol effects (Behnke et al., 2006; Coles & Kable, 1998; Singer et al., 2008).

Exploration of the role of moderating factors provides a greater understanding of the contexts that may exacerbate or ameliorate substance exposure effects. Numerous factors can moderate drug effects, including maternal age (Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004), SES, interventions (Bada et al., 2012; Coles et al., 2015; Frank et al., 2002), genetic variants (Dodge et al., 2014), polydrug exposure (Singer et al., 1994), and gender (Min et al., 2009). While specific drug effects are often small, with effect sizes of .20–.30, the combined effects of exposure with confounded variables can be large. As an example, two decades of research have found that the effects of prenatal cocaine exposure on the cognitive outcome are smaller than those of alcohol or lead exposure, or of the quality of the caregiving environment (Singer et al., 2008). However, the additive effects of these exposures, along with low SES, violence exposure, and other environmental risks often associated with prenatal cocaine exposure, can have a large negative impact on child outcome (Lester, LaGasse, & Seifer, 1998).

The Threat of High and Differential Attrition Rates

The research design must balance the relatively large sample sizes necessary to control for multiple environmental and drug covariates often clustered with opioid use in ascertaining specific drug effects, with practical considerations of available resources. One way to do this is through supporting high rates of retention of participants. For RCTs, a minimal retention rate of 80% is considered acceptable (Gordon, 1985). While historically, many samples of cocaine-exposed infants had significant attrition (Azuma & Chasnoff, 1993; Hurt, Brodsky, Braitman, & Giannetta, 1995), several cohorts were successfully retained into adolescence (Coles, Platzman, Lynch, & Freides, 2002; Richardson, Goldschmidt, Larkby, & Day, 2015; Singer et al., 2018). Attrition remains a major threat to longitudinal cohort studies, as it is often differential, and related to lower SES and family stressors that are more likely to be prevalent in families in which a parent has a substance use disorder (Aylward, Hatcher, Stripp, Gustafson, & Leavitt, 1985; Bender et al., 2003). Sample retention is central to accurate understanding of outcomes and must be considered in research design and implementation. Our experience suggests that studies with high longitudinal cohort retention rates were notable for providing adequate financial incentives, transportation, lunch, and snacks for participants; flexibility of scheduling, culturally competent, nonjudgmental

research staff, access to health, mental health, and social services; and strong relationships with families over time.

Outcome Assessment

Measuring Effects in Infancy and Early Childhood

Assessing outcomes of opioid and other prenatally substance-exposed infants long term is especially important since patterns of effects of fetal teratogens may be transient, continuous, variable, or masked, and may also be exacerbated or fade over time (Coles & Kable, 1998). Since the reliability of the measurement of the target exposure, as well as other substances and risk factors, is most optimal during pregnancy or shortly after birth, most drug exposure studies are initiated in infancy. There are a variety of methods for assessing outcomes at this time. Multiple imaging techniques are now available in the neonatal period in addition to magnetic resonance imaging (MRI), including computed tomography (CT), diffusion tensor imaging (DTI), cerebral Doppler (CD), near-infrared spectroscopy (NIRS) (Barrett, Kable, Madsen, Hsu, & Coles, 2019), positron emission tomography (PET), single-photon and fractional emission computerized tomography (SPECT), and magneto electroencephalography (MEG-EEG), and are increasingly used in developmental studies. EEG recordings and evoked potentials of auditory, visual, and somatosensory responses in infants may provide early indicators of developmental problems in substance-exposed infants (Bakhireva et al., 2015; Kable, Coles, Lynch, & Carroll, 2009; Scher, Richardson, & Day, 2000; Stephen et al., 2017).

In the clinical assessment of behavior, for neonates, the Neonatal Network Neurobehavioral Scale (NNNS) (Lester & Tronick, 2004) has become the most commonly used assessment of infant reflexes and sensory responses in the first month of life, while the Bayley Scales of Infant Development remain (the subject is Scales) the gold standard (Bayley & Aylward, 2019) for older infants. These instruments provide a measure of an infant's current status and may identify those with significant developmental problems. However, infancy scales such as these that rely on sensorimotor functions and social interaction have poor individual predictive validity to later intellectual function (IQ) when done before 2 years of age (Kilbride, Aylward, Doyle, Singer, & Lantos, 2017; McCall & Carriger, 1993). To a great extent, this disconnect is due to the reliance on language development for later cognition. In a study of cocaine exposure, the incidence of cognitive delay based on the Bayley Scale of Mental Development was 2% at 12 months, 12% at 2 years, but 20% by 4 years (Singer, 2001), a trajectory similar to that found with FAS (Coles et al., 1991). These patterns suggest the need for more specific measures that can predict to cognition. With the exception of alcohol, outcome studies of drugs of abuse, including cocaine, marijuana, tobacco, or MDMA, have rarely identified large or global IQ effects. Rather, specific deficits are most commonly noted. Most prevalent are problems in attention (Li et al., 2009; Lupattelli et al., 2019; Noland et al., 2005; Shisler et al., 2016), executive function (Fried & Smith, 2001; Noland et al., 2003), perceptual reasoning (Singer et al., 2008, 2018), working memory (Li et al., 2009; Singer et al., 2008), language (Lewis et al., 2011), and behavior (Hendricks, Malcolm-Smith, Adnams, Stein, & Donald, 2019; Lynch, Coles, Corley, & Falek, 2003; Minnes et al., 2010).

Specificity of Early Deficits and Prediction of Future Performance

Because infancy sensorimotor tasks in the first 2 years of life lack predictive validity for later cognition and because the majority of fetal teratogens are associated with specific rather than global deficits, many experimental tasks have been utilized in infancy to attempt to identify the nature of teratogenic effects as well as to identify those infants at risk for later problems that could benefit from interventions. Among those that have differentiated alcohol or drug-exposed infants from comparison infants are cardiac orienting responses (Kable et al., 2016), visual preferences (Singer et al., 1999), object permanence (Noland et al., 2003), sleep EEG (Scher et al., 2000), focused attention (Shisler et al., 2016), auditory brain stem response (Kable et al., 2009), eyeblink conditioning (Jacobson et al., 2008), and arousal/regulation or reactivity (Schuetze, Eiden, Colder, Huestis, & Leonard, 2018). These infancy tasks are experimental and do not meet requirements for clinical psychological assessments, including standardization, reliability and validity parameters, normative data, and manualization. One exception is the Fagan Test of Infant Intelligence (Fagan & Shepherd, 1989) which assesses visual discrimination and recognition memory and has been sensitive to a wide range of teratogens (Jacobson et al., 1996; Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1985; Jacobson, Jacobson, Sokol, Martier, & Ager, 1993; Singer et al., 2005).

Measurement of Long-Term Effects

At older ages, a broad range of teratogenic functional endpoints can be addressed with numerous psychological tests that exhibit robust psychometric attributes. Most long-term prospective cohort studies of alcohol- and substance-exposed infants developed comprehensive batteries to assess a wide range of cognitive, behavioral, and functional outcomes, using direct assessment as well as caregiver or teacher informant surveys. As research in understanding various effects of teratogens develops, outcome selection transitions from global assessments to more specific focus areas, such as attention and executive function (Coles & Kable, 1998). This transition occurs both because most teratogenic effects are subtle, and also because the subject burden and research expenses are considerable, as the dynamics of confounding or moderating environmental factors also need to be considered. Adolescent and early adult outcomes of importance are primarily functional, i.e., academic achievement, sexual risk behavior, substance use and mental health disorders, physical health, delinquency, incarceration, and ability to maintain a job. A significant issue is that, to date, with rare exceptions (Richardson et al., 2015; Singer, 1997; Streissguth et al., 1986), cohorts have not been followed to adulthood, for numerous reasons, including poor retention and changing federal funding priorities. The variability of assessment instruments across individual outcome studies remains a barrier to timely understanding of prenatal substance exposure effects and communication of risk to the public. Harmonization of outcome assessments across sites in multisite studies would be of great benefit to more rapid determination of the risk profile of specific substances.

Political and Ethical Contexts

Stigmatization of Substance Using Pregnant Women and Their Children

All scientific research is embedded in the social, governmental, and ethical contexts of their times, but research on prenatal alcohol and substance exposures is particularly affected. The

impact of these contexts is perhaps most notable in the differences between research and treatment during the cocaine epidemic of the 1980s in comparison to today's opioid epidemic. Alarming media reports based on a few case studies raised public awareness of the cocaine epidemic in a way that produced damaging stereotypes of exposed infants. Newspaper headlines such as "Crack Babies Turn 5 and Schools Brace" (Chira, 1990) and "Drug Addicted Toddlers are Raising Havoc" (Honolulu Advertiser, 1990) may have raised public awareness and perhaps stimulated federal funding for developmental studies. However, these damaging labels were soon disproved since distinct sequelae that could be linked to cocaine exposure, although significant, were small (Coles, 1993). Despite these findings, punitive public policies on multiple fronts characterized governmental and social responses to the cocaine epidemic (Paltrow et al., 2000; Rubenstein, 1991). Such policies made and continue to make research into prenatal exposures much more difficult given the very real risk of incarceration and potential loss of child custody for the pregnant woman. Governmental and social responses to the opioid epidemic have been less punitive and more focused on treatment, which some attribute to racial and demographic differences between the epidemics (Neuspiel, 1996). However, the stigma of alcohol and drug addiction remains a prominent issue (Corrigan et al., 2017; Corrigan et al., 2018; Room, 2005; Volkow, 2020) even among healthcare providers, with some state policies continuing to treat these diseases criminally rather than medically.

Ethical Responsibilities for Researchers

This cultural context raises ethical issues for researchers. Most investigators initiate studies to support the scientific understanding of the effects of exposure. However, most also intend that their work will be of benefit to pregnant women and to their children. Therefore, it is important to avoid any actions that will cause harm to these vulnerable individuals. The researcher has to be cognizant of any legal or social risk that participation in the research may bring to the participants. It is questionable for instance, whether learning that a particular drug has a small effect on a child, can be worth children being placed in foster care and their mothers incarcerated, actions from which the effects may be a great deal larger. Similarly, it is important for the scientist, in releasing findings and in talking with the media about research results, to place these in the proper context. The notorious "crack babies" are an excellent example (Coles, 1993). They were purported to be severely impaired, when actually, there were no physical effects and little evidence of significant cognitive effects that could not be attributed to various covariates. Whether those who promoted the image of the "crack baby" did so out of inexperience or whether they were influenced by the possibility of publication and grant funds or were simply caught up in the frenzy, a great deal of damage was done to women and children. It is important that, in any new investigation, we learn from such experiences.

Implications for Future Research

All research success depends on the work of those who have gone before. For that reason, it is important to take into consideration the many previous efforts to understand how prenatal exposures affect the development of children. In the current issue, previous research has been reviewed and recommendations made based on this experience that can be valuable for

the planning of future studies. Beasley et al. (this volume) describe how pregnant and postpartum women at risk of substance use can be engaged in longitudinal research. Croff et al. (this volume) provide a design framework for the collection and analysis of biospecimen collection in such studies. Morris et al. (this volume) set forth the principle for guidance in the selection of assessment measures for child outcomes. Finally, Bakhireva et al. (this volume) discuss the inclusion of disadvantaged populations (specifically Native American and Alaskan Natives) in large national studies. These papers provide specific guidance for the initiation of future studies.

Summary and Conclusions

The statement “We are the drug habit nation” was made by chemist H.W. Wiley in 1911 (Jonnes, 1996; Room, 2005) and remains true today. Wiley’s comment referred to what was considered America’s first drug epidemic, occurring between 1885 and 1925, encompassing cocaine, alcohol, and opiates in the form of patented medicine with morphine or heroin, and including popular opiate or cocaine-enhanced wines and public opium dens. It is estimated that in 1900, 1 American in 200 was an opiate or cocaine addict (Jonnes, 1996). Various waves of drug popularity and decline or legality and illegality have waxed and waned over the century since the first antidrug laws were passed (consider prohibition and the current legalization of marijuana). In each wave and continuously, exposures are affecting fetal development and child outcomes in unknown ways.

In the opioid epidemic of the 1970s, considerable knowledge was generated about the effects of heroin and methadone on the fetus and the management of NOWS, an opioid withdrawal syndrome that had been noted medically since the late nineteenth century (Happel, 1900). However, research efforts declined as new epidemics emerged, until the opioid crises of this generation exploded. The opioid epidemic may already be giving way to new cocaine and methamphetamine epidemics. Recognition of the continuous and pervasive use of addictive substances in our “drug habit nation” should lead to a broad scientific effort to understand how each of these substances affects child development, as well as spur prevention and intervention programs for those proven to be harmful.

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