

# ADVANCES AND REDIRECTIONS IN UNDERSTANDING EFFECTS OF FETAL DRUG EXPOSURE

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## INTRODUCTION

Although the massive crack-cocaine epidemic of the late 1980s and early 90s has subsided, its effects persist in the large numbers of children, estimated in the hundreds of thousands (U.S. Department of Health Services 1993), who were born with prenatal exposure and are now at preschool or school age. Recent (U.S. Department of Health Services 1996) survey data indicate that, although the epidemic has subsided, it has not vanished. The percentages of women of childbearing age indicating cocaine use in urban areas for the previous year were 4.3 percent and 2.8 percent for white and black women, respectively, from 25 to 29 years of age, and 1.8 percent and 4.9 percent, respectively, for white and black women ages 30 to 44. Determination of the extent and nature of the sequelae of fetal cocaine exposure is the focus of the large scale, longitudinal studies presented in this special section of the *Journal of Drug Issues*. Their importance lies not only in what these studies will tell us about the outcomes of the first generations of affected children, but also in how their findings will help shape future research, public policy, prevention, and intervention efforts. Moreover, findings from the reports highlighted in this special section are useful in informing the design of studies of other drugs, such as heroin and methamphetamine, which may supplant cocaine as drug trends fluctuate.

Both Richardson's and Carmichael Olson's studies illustrate the necessity of controlling, either by design or statistical analysis, for the large number of confounding variables which plague longitudinal developmental studies (See Singer 1998). Their studies and many others have by now established the clusters of risk factors linked to maternal cocaine use. These risks include older maternal age, single marital status, poverty, lower educational level, greater exposure to violence, larger numbers of siblings, higher maternal psychological distress, infant placement out of home, prematurity, and low birthweight. Given this

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clustering of risk factors, it is by now clear that the use of small samples of convenience, which may have had heuristic value at earlier stages of research, add little to the existing base of knowledge about fetal cocaine effects. These new generation studies demonstrate the need for conformity in controlling for confounding factors, as well as the need for adequately large sample sizes and appropriate statistical methods to account for these other risk factors in estimating effects of fetal cocaine exposure.

Careful definition of the selection criteria and recruitment biases of individual cohorts, as well as documentation of attrition rates and biases, are also needed if any consensus is to emerge from the studies underway. This level of rigor is especially important since findings from these studies will be used to develop public policies regarding the needs of drug-exposed children, and thus, these studies have considerable political and legal ramifications. Journal editors should insist that these data be provided, since otherwise it is not possible to evaluate whether, given any study's design characteristics, Type I or II error is more likely. Some studies (e.g. Singer et al. 1999) have found that infants more likely to be seen for follow-up within the window of time acceptable for a neonatal assessment were at lower risk based on demographic and medical characteristics than those not seen, resulting in a bias toward not finding effects which may actually exist. Alternatively, at later ages, it is equally plausible that those children with more salient risk would be identified by medical or social service providers and retained for follow-up, perhaps predisposing to finding more severe cohort effects than actually occur. Either possibility influences whether cocaine exposure effects are more or less likely to be detected and, thus, need to be considered in interpreting study findings. Jacobson and Jacobson (1995), however, have pointed out that, in the early stages of research into a potential teratogen's effects, there should perhaps be greater concern about the occurrence of Type II error, given the danger of public complacency which might be engendered toward a harmful substance by studies with a bias towards Type II error.

The importance of establishing whether intervening variables are confounders or mediators of drug effects has also become apparent in these new studies (See Jacobson and Jacobson, 1999). Mediating variables are those hypothesized to be causally influencing, rather than confounding, the outcome of interest. Prematurity and low birthweight have been identified as potential mediators of cocaine's and other drugs' effects, since numerous studies have now established strong associations between cocaine exposure and these outcomes (Zuckerman et al. 1989; Singer et al. 1994, 1999; Eyler et al. 1998) as well as linked them to known physiologic mechanisms of cocaine's effects (Wood et al. 1987). Many studies of cocaine effects have restricted their samples to full-term births, in order to separate out effects of cocaine exposure vs. prematurity. While such separation provides necessary information about cocaine or associated drug effects in full term infants, these studies may underestimate the extent of possible effects of fetal cocaine exposure for the population at large. Our cohort, for example (see Arendt, this issue), which was recruited from a hospital population of all exposed infants identified over a two year period, had a 28 percent rate of prematurity for the exposed group, twice that of the comparison group. It would be important not to underestimate effects of fetal cocaine exposure when studies have excluded a

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significant proportion of the affected children. Brown and colleagues (1998) for example, found differential effects for physiologic and behavioral outcomes of fetal cocaine exposure based on degree of prematurity. Future studies will need to establish the interrelationships among prematurity, low birthweight, and drug exposure factors more specifically.

A variable of particular interest in studying the effects of fetal cocaine exposure is that of maternal psychological distress or psychopathology, because it can reasonably function as both a confounder and a mediator of cocaine's effects on child development. High rates of depression, phobic anxiety, paranoid ideation, antisocial personality disorder, and post-traumatic stress disorder have been identified among female cocaine users (Griffin et al. 1989; Singer et al. 1995; Weiss et al. 1989; Woods et al. 1993), and these mental health disorders have been linked to poorer child outcomes independent of drug exposure (Singer et al. 1997). For example, in non-exposed newborns whose mothers were identified as depressed in mood style at birth, early dysregulation in sleep-wake behavior and differences in various psychological and biochemical measures have been identified in comparisons with infants of non-depressed mothers (Field 1995). Non-drug exposed newborns born to mothers who were depressed during pregnancy have also been found to be more fussy and less consolable (Whiffen and Gottlieb 1989; Zuckerman et al. 1991) and to perform more poorly on the Brazelton Neonatal Behavioral Assessment Scale (Abrams et al. 1994). Many of the sequelae seen in infants of depressed mothers overlap substantially with those recently described in cohorts of cocaine exposed neonates (Eyler et al. 1998; Coles et al. 1992; Chasnoff et al. 1989), raising the question of the relationship of fetal cocaine exposure and maternal psychopathology with neonatal behavioral outcomes.

The co-morbidity of mental health and substance abuse disorders has been well established, with estimates that approximately 40 to 50 percent of substance abusers have a concurrent mental health diagnosis (Kandel et al. 1998; Kessler et al. 1996; Peindl et al. 1998). A number of epidemiologic and clinical studies have been undertaken to attempt to determine whether certain affective or other psychiatric disorders pre-exist and are likely to precipitate alcohol and/or drug addictions, with mixed findings (Merikangas and Stevens 1998; Brooks et al. 1998). While it is unlikely that all pregnant women using cocaine have pre-existing major psychiatric disturbances, it is likely that a significant subgroup of users have such contributing disorders and that the offspring of addicted mothers with such disorders are at greater developmental risk due to genetic and biochemical factors. Additionally, long-term cocaine addiction itself has known neurologic and psychologic effects on users (Gawin 1991). These maternal psychological sequelae, whether due to primary psychiatric disorders or secondary to addiction, appear to have effects independent of fetal drug exposure on child cognitive outcome within the first two years of life (Singer et al. 1997). Minnes et al. (1997) demonstrated that maternal psychological distress and impairments in executive functioning mediated the relationship between heavy cocaine use during pregnancy and more negative maternal affective interactions with her infant after birth. Thus, the relationships between maternal psychological distress, cocaine use during pregnancy, maternal parenting behaviors, and child

outcomes are complex and require greater clarification if we are to achieve a better understanding of the biologic effects of fetal exposure.

Perhaps even more difficult to disentangle are the effects of cocaine exposure on the developing child versus those of other drugs. As shown in the studies presented, users of crack-cocaine during pregnancy are almost invariably regular users of additional drugs, especially tobacco, alcohol, and marijuana. Moreover, the heaviest cocaine users are also the heaviest users of other drugs (Singer 1999; Richardson, this issue; Eyler et al. 1998). In Richardson's study (this issue), it was not possible to demarcate a group of cocaine users that did not use alcohol. Similarly, in our cohort in Cleveland (Singer 1999; Arendt, this issue), 98 percent of cocaine users also used tobacco, and in significantly higher amounts, than non-users. While cohorts of habitual users of *only* tobacco, marijuana or alcohol during pregnancy can be isolated, the vast majority of cocaine-exposed infants are subjected to the additive or interactive effects of an unknown proportion of multiple drugs, some combinations of which may have unique effects. Cocaethylene, for example, is formed through the combined use of cocaine and alcohol and has been related to stunting of fetal growth in animal studies (Church et al. 1991). In human studies, infants of women who used cocaine and alcohol concurrently during pregnancy were shorter in length at birth than those whose mothers used only one or the other drug (Singer et al. 1994). Similarly, infants exposed to both cocaine and tobacco, or marijuana and tobacco, had poorer scores on a neonatal measure of alert responsiveness than those exposed to only one substance (Eyler et al. 1998).

Earlier studies defined cocaine exposed samples and drug confounders into dichotomous use/non-use categories, a practice which may have had the effect of obscuring sequelae which occur only at higher thresholds. In contrast, second generation studies have progressed towards using multiple measures of drug exposure and have attempted to describe timing and severity of exposure for cocaine and confounding drugs as reliably as possible. Of course, this is quite difficult to do retrospectively for an illegal drug with no standard unit of measurement! Nevertheless, an increasing number of studies have now identified adverse cocaine effects when severity of exposure has been measured through quantity or frequency measures or through dividing cohorts into heavy/light exposure categories (Alessandri et al. 1998; Eyler et al. 1998; Jacobson et al. 1996; Richardson et al. 1996; Singer et al. 1999).

Arendt's study (this issue) provides an illustration of how the addition of a quantified measure of several cocaine metabolites in newborn meconium (ng/gm) can influence assessment of severity of fetal exposure and add to the reliability of estimates of severity of exposure. In this study, addition of the meconium measure to screening resulted in only slight improvements in identification of cocaine-exposed infants, as 100 percent were already identified through urine screens and/or self-report interviews (Although meconium measures may be more useful in identifying infants in a non-research setting). However, the addition of meconium measures significantly changed the classification of an infant based on severity of exposure, with 52 infants (36 percent of the cocaine-exposed sample) reclassified as heavily exposed who would have been classified as lightly exposed if only maternal self-report interviews were utilized. In any study, if a significant proportion of heavily exposed infants are misclassified as lightly exposed,

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differences between heavy and light groups can be obscured and/or detection of differences between heavy and non-exposed groups may be diminished due to loss of power.

There are acknowledged limitations to the reliability and validity of the use of meconium samples to quantify severity of exposure. Meconium does not form until the last two trimesters of pregnancy and cannot be used to detect exposure during the first trimester. Only a few laboratories currently provide quantification of cocaine's metabolites as well as metabolites of other licit/illicit drugs (Ostrea et al. 1989; Lewis et al. 1994), and the question of whether quantification is reliable and valid remains open. In our sample, the amount of cotinine, a metabolite of tobacco, was unrelated to maternal self-report of quantity of tobacco used, for example. Meconium assays for cocaine metabolites have also been criticized for the high likelihood of their contamination with urine in newborn diapers (Lombardero et al. 1993).

Nevertheless, Arendt et al's study (this issue) found a significant and reasonably high association between maternal self report measures of severity of cocaine use and cocaine metabolites in newborn meconium. Moreover, several papers have now been published which demonstrate reliable associations between quantified measures of cocaine metabolites in meconium and more adverse child outcomes (Tronick et al. 1996; Mirochnick et al. 1995; Singer et al. 1999; Delaney-Black et al. 1996). While these studies have all measured benzoylecgonine, cocaine's primary metabolite, the measurement of other cocaine metabolites, including cocaine, cocaethylene, and m-OH-benzoylecgonine also holds promise (Singer et al. 1999). In one study (Singer et al. 1997), the quantity of cocaethylene in meconium was the only cocaine metabolite to be reliably associated with attentional abnormalities, suggesting that either concurrent cocaine and alcohol exposure, or alcohol exposure alone, has effects on this behavior in the neonatal period. Hair analysis is another technique that continues to be refined. Correlations of maternal and fetal concentrations of cocaine metabolites in maternal and infant hair (Grant et al. 1994) have been found with assumed dose during pregnancy (Forman et al. 1992) and with levels of exposure (Chiriboga et al. 1999). To date, the lack of a physical marker of chronic alcohol use has hampered efforts to delineate specific thresholds for risk which could aid public health efforts to prevent fetal alcohol syndrome and alcohol related birth defects. In a recent study, the presence and amount of fatty acid ethyl esters (FAEE) in the blood of postpartum women was linked to their report of alcohol use during pregnancy (Bearer et al. 1999). As the refinement of these and other biomarkers progresses, and as they are studied in regard to their relationships with biobehavioral assessments, they will greatly enhance ascertainment of the developmental risks posed by potential neurobehavioral toxins.

Some of the perplexing statistical questions that arise in the large scale longitudinal studies necessary to investigate prenatal cocaine effects have been raised in Richardson's paper. To date, all outcome studies published, despite their longitudinal designs, have relied on single age outcome points or standard repeated measures ANOVAs in reporting data. Because of the high rates of attrition in studies of drug exposed populations, in many studies 30 to 50 percent, findings from only one follow-up age are often misleading, and standard repeated

measures analyses require that data from many subjects be discarded. The use of newer mixed model analytic strategies, which utilize all data points and estimate missing data, such as hierarchical linear modeling (HLM), SAS PROC MIXED, and generalized linear equation modeling, offer greater power, more confidence in interpreting findings, and can accommodate data on subjects that were seen outside the typical longitudinal age window (Francis et al. 1991).

In addition to the problem of multicollinearity described by Richardson (this issue), the major independent variable of interest in studies of cocaine exposure, i.e. severity of drug use, usually departs substantially from assumptions of normality. The standard methods of analyses used commonly in drug exposure studies (ANOVA, Pearson product moment correlation and least squares regression) have been criticized as non-robust because of low power under conditions of non-normality (Wilcox 1998). Newer rank-based methods of analysis have been proposed to handle these distribution problems, and other problems, such as outliers (Wilcox 1998).

Other investigators (Jacobson and Jacobson, in press) have raised the issue of the difficulty of determining threshold values in studies of adverse effects of toxic substances through use of standard parametric statistical techniques. They have proposed the use of nonparametric regression (Hasti and Tibshriani 1990) or hockey stick regression, which have yielded threshold levels in alcohol effects in exploratory analyses of their longitudinal data sets.

The importance of masked examiners in assessing developmental sequelae of fetal exposures is extensively justified by Eyler and colleagues (this issue). The effects of observer biases on assessment of behavioral outcome has now been well documented, especially in the case of the prematurity stereotype (Stern and Hildetandt 1986). Perhaps in no study is control for such biases more important than in the case of the "crack baby" who received so much negative and inflammatory media coverage (Mayes, Granger, Bornstein, and Zuckerman 1992). Despite the stringent safeguards imposed by Eyler and her group, it appears that significant biases still pervaded examiners' perceptions. While some of those perceptions may actually have been embedded in fact, others may have stemmed from prejudicial stereotyping. In our studies in Cleveland, it has been difficult to mask examiners when a caregiver is overtly behaving in an unusual manner or the caregiver is obviously not the biological mother, and testing older infants requires the presence of the caregiver. Longer term follow-up will provide data less likely to be contaminated since the child and his/her examiner can be maintained completely separately from the caregiver. The use of biologic quantified measures and the separation of samples into light and heavy users have also provided some safeguards. We have found that light and heavy users in our sample did not differ on many social and birth covariates and that masking staff to severity of use was more easily accomplished than masking to cocaine status.

In summary, the past decade of research has produced significant advances in our understanding of methodologic issues in outcome studies of fetal cocaine exposure. Greater specification of important covariates of exposures which may influence child outcome can help identify the most vulnerable populations and potentially provide avenues for intervention, as well as lead to the design of more methodologically rigorous research studies. The refinement of quantifiable biologic and self-report measures of severity of various drug exposures and the

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use of modern statistical techniques promise greater sensitivity to potential effects of drug exposure. Attention to examiner biases and the need for masking will help assure the integrity of future findings.

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