Exhibit C

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EDITORIAL

The Effects of Cocaine and Amphetamine Use During Pregnancy on the Newborn: Myth versus Reality

The fact that some women use and abuse substances during pregnancy is a source of great consternation and concern in science and in society. The knowledge of the harm associated with drug consumption for the mother lead one to assume that it must be worse for the developing fetus and newborn. Although the past few decades have seen a growth in both the number and quality of studies, there remains a gulf between myths of prenatal substance exposure and scientific evidence of fetal and newborn effects.

Two myths appear particularly persistent: that drugs cause birth defects and that women who use drugs are unfit to be parents. These myths were in evidence by a recent article in this journal, "Addiction in Pregnancy,"[1] which was part of the Special Issue: Women, Children and Addiction. In the article, Keegan et al. state that cocaine and amphetamines "can lead to congenital anomalies" and that "from a social-focused and family-focused standpoint, the use of cocaine is extremely problematic [as] evidence of cocaine usage in pregnancy often results in the removal of the infant from maternal custody within the first 18 months of life." Statements such as these abound in the literature on pregnancy and addiction. They are at best grossly misleading, arising more from bias and prejudice than from the scientific literature. However, their persistence is fascinating and best understood within the context of the crack cocaine "epidemic." Before refuting these myths, we will review the history of crack cocaine and pregnancy to highlight lessons learned from the cocaine literature, lessons that can be applied to current research on methamphetamines and pregnancy.

A BRIEF HISTORY OF CRACK COCAINE AND PREGNANCY

Current research on drug use in pregnancy operates in the uneasy legacy of the crack cocaine panic. Although the term "crack baby" did not enter into the public lexicon until the late 1980s, interest in the prenatal effects of cocaine arguably began in 1985 with the publication of an article by Chasnoff et al. in the *New England Journal of Medicine* describing the outcomes of 23 cocaine-using pregnant women detailing a higher incidence of placental abruption, congenital anomalies, and poorer measurements among the infants by the Brazelton Neonatal Behavioral Assessment Scale.[2] Interest in the topic grew rapidly and succeeding studies documented similarly catastrophic outcomes, such as fetal death,[3] Sudden Infant Death Syndrome (SIDS),[4,5] cerebral injury,[6,7] as well as congenital anomalies,[8] such as genitourinary tract malformations[9,10] and cardiac anomalies.[11] Newborn outcomes described were also dismal including seizures,[12] hearing impairment,[13] and difficulties in early language development[14] and motor performance.[15] Most concerning was

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research that suggested that prenatal drug exposure threatened maternal attachment.[16]

These scientific findings fueled a media panic and gave credence to the public reporting of "crack babies" as physically damaged and emotionally stunted.[17] Public policy and perception shifted as a consequence and the war on drugs was expanded with struggles ensuing over the criminalization of drug use in pregnancy.[18]

Crack cocaine exposure in pregnancy offers a cautionary tale of the role scientific enquiry plays in the formulation of public problems. Beginning a decade after Chasnoff's initial publication, systematic reviews and meta-analyses problematized the poor pregnancy and newborn outcomes initially described. Overall, when outcomes of cocaine-exposed pregnancies were compared with other drug-exposed pregnancies, the observed effect of cocaine greatly diminished. For example, Fares et al. demonstrated an increase in SIDS among cocaine-exposed newborns only when compared with drug-free and not with polydrug-exposed newborns.[19] Similarly, in a meta-analysis of 33 studies, Addis et al. concluded that only placental abruption and premature rupture of membranes were related to cocaine use. They found no effect of birth defects on congenital malformations or birth weight.[20] Finally, Frank et al. in a review of 74 articles concluded that there was no convincing evidence of developmental or behavioral outcomes among children aged 6 or younger with prenatal cocaine exposure, although some subtle differences were noted.[21] These analyses point to the role of unmeasured confounders, such as cigarette smoking, in the early literature. In addition, they highlight problems in study design, in particular the lack of adequate control groups and an absence of blinding.[22]

The absence of evidence is not always the evidence of absence. Meta-analysis of observational data especially is subject to the effects of study heterogeneity and in the pooling of disparate data subtle effects can be lost. This is no small concern as in the context of cocaine exposure, even small effects at birth can be of measurable consequence over time.[23] Because randomized studies are unethical, well-designed cohort studies are critical in exploring causality. Established in the early 1990s the Maternal Lifestyle Study (MLS) is a longitudinal cohort study designed to explore the effects of prenatal cocaine exposure on child outcomes.[24] The cohort includes 658 exposed and 730 comparison mother/child dyads, the children of which are currently in their adolescence. The MLS data comprises the best data on the effects of cocaine on child development. Its many publications suggest that the effects of cocaine on development are subtle and inconsistent and need to be understood in the context of polydrug use, as well as within the caregiving environment.

METHAMPHETAMINE RESEARCH: LEARNING FROM THE MISTAKES OF CRACK?

Methamphetamine use is now more common than cocaine use in pregnancy, and its use by women of childbearing age is increasing.[25–27] Methamphetamine has become the primary substance compelling drug treatment during pregnancy.[28] In the early part of the decade, media coverage of methamphetamines in pregnancy took the unfortunately familiar tone of alarmist labeling and calls for punishment rather than treatment. In response to such coverage, on July 25, 2005, more than 90 physicians and scientists drafted a consensus statement titled "Meth Science Not Stigma" and sent it to the major news outlets (http://www.jointogether.org/resources/pdf/Meth_Letter.pdf). The letter called on the media to refrain from using pejorative terms such as "meth babies" and requested that media coverage (and legislative proposals) be "based on science, not on presumption or prejudice."

Another lesson learned from the crack cocaine experience was the importance of well-designed, prospective studies in illuminating the sequelae of prenatal drug exposure. Modeled after the MLS, Lester et al. initiated the Infant Development, Environment, and Lifestyle (IDEAL) study in 2002 to study the effects of prenatal methamphetamine exposure.[29] Investigators have enrolled 1,618 mothers at four clinical centers in cities where methamphetamine use is problematic. Thus far, the results from the

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IDEAL study indicate that methamphetamine is associated with fetal growth restriction,[29] but no measurable difference in psychological functioning by age three.[30]

Luckily, we seem to be learning from the past. Longitudinal studies such as IDEAL will continue to provide essential data regarding the effects of methamphetamine during pregnancy. However, subtle biases and problematic study design continue to exist in these subject areas, which perpetuate particular myths of exposure.

MYTH: COCAINE AND AMPHETAMINES CAUSE BIRTH DEFECTS

The possibility of adverse events from drug-exposed pregnancies only emerged after the congenital rubella epidemic and the thalidomide tragedy, which replaced the concepts of the "placental barrier" and "fetal invulnerability" with that of teratogenicity.[31] Since then, many drugs have been assumed to be teratogens, and it is especially common for research on drugs of abuse to begin with the assumption of teratogenicity.

This assumption and misconception of teratogenicity was furthered in a recent article in this journal that stated that both cocaine and amphetamines "can lead to congenital anomalies."[1] The evidence cited consists of case reports and animal models. Given the evidence base on cocaine in pregnancy including well-designed cohort studies, such as the MLS, and systematic reviews (none of which have shown an association with cocaine and anomalies), the use of case reports is misleading and not representative. Animal studies are important in the research on toxic effects. However, the generalizability of their results to human drugs of abuse is limited. Not only are animals given far larger doses of the substances, but there are important differences in the biology of reproduction between species that can impact the interpretation of animal research. The length of fetal development differs between species, as does placental function. For example, the human placenta has a far greater capacity to metabolize drugs/cocaine than a rats.[32] Although much remains unknown about the effects of in utero methamphetamine exposure, no consistent teratological effects on the developing human fetus have been identified.[33–43] Overall, prenatal methamphetamine exposure does not seem associated with any consistent increase in congenital anomalies above the background 3% population risk.

MYTH: COCAINE OR METHAMPHETAMINE IMPAIR MOTHERING

The assumption that women who use drugs are impaired in their ability to mother displays a complex and deep bias in our society. Keegan et al. state that "from a social-focused and family-focused standpoint, the use of cocaine is extremely problematic [as] evidence of cocaine usage in pregnancy often results in the removal of the infant from maternal custody within the first 18 months of life."[1] Statements such as these question the very legitimacy of motherhood among women with addictions. The concept of impaired maternal fitness due to drug use received much attention during the crack cocaine "epidemic," with the most extreme leading to calls for forced sterilization of women with addictions. However, there is no evidence that maternal addiction is worse on family structure than other mental illnesses. In fact, maternal-infant interactions appear to be less positive when the mother is severely depressed, an observation compounded by poverty.[44] Ethnographic data contradicts this assumption of maternal fitness as well. In their classic study "Pregnant Women on Drugs," Murphy and Rosenbaum detail how the desire for children is often the only normative cultural practice available to women with addictions.[45] Other ethnographic work supports this observation and further describes care these women invest in their maternal duties.[46]

CONCLUSION

The perpetuation of myth in the face of scientific evidence arises from biases (often unexamined) on the part of researchers. The use of substances by pregnant women can be an emotional

topic. However, research should be guided by evidence, and an awareness of previous pitfalls in the topic area is essential to avoid committing the same errors. Beyond the lack of evidence for teratogenicty, the persistence of this hypothesis of absolute harm in the literature serves to justify further condemning women who use during pregnancy. So too is the implication of impaired maternal fitness: these women do not deserve to be mothers.

There is nothing categorically different about addiction in pregnancy compared with addiction in general. Pregnant women who use drugs are women who use drugs, get pregnant, and cannot stop using drugs. The fact that they are condemned in society leads to their further marginalization, which does nothing to improve their lives or the lives of their children. Science, good responsible science, is needed to inform concrete interventions and public policy such that the harms of addiction are minimized and maternal, child, and public health expanded.

Mishka Terplan, MD, MPH, FACOG
Department of Obstetrics, Gynecology & Reproductive Sciences,
Department of Epidemiology and Public Health
University of Maryland School of Medicine
Baltimore, MD 21201
E-mail: mterplan@upi.umaryland.edu

Tricia Wright, MD, MS, FACOG
Department of Obstetrics, Gynecology & Women's Health
University of Hawaii
John A. Burns School of Medicine
Honolulu, HI 96826

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