Translating Basic Research on Drugs and Pregnancy Into the Clinical Setting

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INTRODUCTION

Drug abuse has become a major problem within the field of obstetrics and gynecology. At the University of Rochester, investigators in the fields of obstetrics and pediatrics surveyed the community and found about a 5.5-percent incidence of cocaine use, but when neonatologists selectively screened high-risk babies, the positivity rate for cocaine was more than 20 percent (Ryan et al. 1994). Perhaps no other condition in high-risk obstetrics is more prevalent. Drug abuse should be a topic in which all obstetricians are interested.

Great changes have occurred in this field in the past 10 years. Drug abuse is not just a condition of underserved populations or any particular minority group; it involves all segments of society.

COMMUNITIES AT RISK

Drug abuse and pregnancy is a complex area. Although drug abuse is the main concern, many pregnant women live in communities where fear, sexual and other physical abuse (including rape), and poverty are interwoven. Certain drugs were believed to have disappeared in these communities, but they have returned. In the recent past, University of Rochester Medical Center (URMC) obstetric residents had experience with patients who were using heroin and methadone, but during the past year in Rochester, snorted heroin appeared at a purity rate of around 50 percent, unlike the 4 or 5 percent previously used in intravenous (IV) injections of heroin.

This new trend has rekindled old questions that were never answered. Should pregnant women who are on heroin be detoxified during pregnancy? How should the fetus be monitored? What aspects of fetal health should be monitored? The author's laboratory has generated interesting observations about cocaine's actions in pregnancy, and the

author and colleagues have collaborated with other researchers to study obstetrics and drug abuse. The laboratory has shown that the animal model is an important resource for mechanistically evaluating the effects of illicit drugs on the developing fetus.

LABORATORY FINDINGS

In the laboratory, clinical observations have been used to develop specific hypotheses. The studies that test these hypotheses can assist in making more astute clinical observations and posing valid clinical questions. This interaction between the basic science laboratory and the clinical setting must be strengthened. Data from several laboratories have created a picture of how cocaine interacts with the maternal-placental-fetal unit. For example, during pregnancy, cocaine stimulates the maternal heart and causes reduced uterine blood flow through constriction of the uterine blood vessels. Because the uterine vessels are normally widely dilated, with a high blood flow rate, this vascular bed is a prime target for cocaine's actions in pregnancy. Thus, cocaine produces a decrease in uterine blood flow while the maternal heart rate, blood pressure, and cardiac output increase (Woods et al. 1987, 1994).

Unfortunately, this cocaine-induced blood pressure increase is transmitted into the delicate blood vessels within the placenta. In sheep, these findings are consistent with an early report of an increase in miscarriage with cocaine use (Chasnoff et al. 1985). Numerous incidents of abruptio placentae have occurred as a result of cocaine use among pregnant women in the U.S. population.

Cocaine also decreases oxygen delivery to the fetus, resulting in the release of norepinephrine and epinephrine. However, cocaine passes so quickly across the placenta that within 2 minutes, the cocaine level in the fetus is comparable to that in the mother (Woods et al. 1989). Unfortunately, cocaine blocks the normal removal of norepinephrine in the fetus, just as it does in the adult. Consequently, the fetus exhibits hypertension that is even greater than if the fetus were made hypoxic in the absence of cocaine exposure.

Cocaine also affects the fetus in other ways. Owiny and colleagues (1991) have shown that fetal lambs exposed to maternal cocaine demonstrated an increase in adrenocorticotropic hormone and cortisol. Chan and associates (1992) have demonstrated that norepinephrine is

released by the fetus during cocaine exposure, a process that explains the rise in blood pressure. Epinephrine is released more slowly and probably accounts for the delayed increase in heart rate. Hurd and colleagues have written several papers that address the issue of cocaine-induced preterm labor (e.g., Hurd et al. 1993; Smith et al. 1995). Chronic cocaine exposure may either downregulate beta receptors in the uterus or unbalance the relationship between adrenergic receptors. Many institutions use beta agonists as the primary drug to stop preterm labor, but in pregnant cocaine users, the uterus may respond poorly to that type of drug.

The fetus is not the only target for cocaine; maternal risks also are significant. Cardiac arrhythmias occur in pregnant sheep administered IV cocaine (Woods and Plessinger 1990). The normal heart rhythm suddenly exhibits atrioventricular disassociation and ventricular tachycardia before returning to a sinus rhythm. These cardiac changes in sheep do not differ significantly from the electrocardiogram findings in human adult cocaine addicts as reported by Isner and colleagues (1986). Of even greater concern is that pregnancy may predispose the mother to enhanced cardiotoxicity from cocaine that is not apparent in the nonpregnant state (Woods et al. 1994). These findings suggest that hormones during pregnancy may interact to enhance cocaine's cardiovascular actions.

If cocaine produces a rise in maternal epinephrine and norepinephrine that increases the heart rate and blood pressure, this may increase myocardial oxygen demand as well. However, if, as has been shown in nonpregnant animals, cocaine restricts coronary blood flow that normally would increase to meet the needs of increased myocardial function, this impaired response, coupled with cocaine's ability to block sodium channels, may lead to arrhythmia and even death.

The author and colleagues found that fetal exposure to cocaine is not simply through maternal-to-fetal transfer. Sandberg and Olsen (1992) administered cocaine subcutaneously to guinea pigs every day for 10 days and sampled the amniotic fluid, fetal plasma, and maternal plasma on the last day. Cocaine concentrations in amniotic fluid were significantly higher than in maternal and fetal plasma.

As a followup to these findings, the author and coworkers administered cocaine directly into the amniotic fluid of animals that had not been previously exposed (Mahone et al. 1994), which demonstrated

that cocaine can enter the fetal circulatory system at about 3 to 5 percent of the concentrations in the amniotic fluid. When the trachea was occluded in some of these fetuses, detectable fetal blood levels were still found. Cocaine's entry into the fetus was not simply from swallowing; cocaine in the amniotic fluid appeared to enter the fetal circulation through the placental vessels or the umbilical cord. Amniotic fluid may act as a drug reservoir to consistently expose the fetus to drugs, even after the mother demonstrates a drug-free state.

CONTRADICTORY FINDINGS?

Researchers disagree about the risks of cocaine use during pregnancy. Dixon and Bejar (1989) suggested that cocaine-exposed babies were being diagnosed with brain lesions in as much as 20 to 25 percent of cases, but later studies failed to confirm these findings. Laboratory observations are only a starting place to ask general questions. Cocaine-exposed babies likely are not neurologically impaired to the degree initially reported, even when they are exposed throughout most of the pregnancy. However, there is still reason for concern. Case reports show that cocaine has other lethal effects. For example, Burkett and colleagues (1990) described a 26-year-old woman, 7 months pregnant, who came to the emergency room unconscious, without blood pressure or respiration. An electrocardiogram showed severe bradycardia. After an unsuccessful attempt at resuscitation, doctors performed a cesarean section, and a placental abruption was noted. Analysis of maternal plasma levels demonstrated the presence of cocaine. The mother died.

A report by Pollock and coworkers (1991) indicated that 75 percent more cocaine-related deaths were reported to the Drug Abuse Warning Network (DAWN) than to the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS). From 1983 to 1988, NCHS data from 25 metropolitan areas indicated that there were 3,466 cocaine-related deaths, whereas 6,057 cocaine-related deaths were reported to DAWN. Underreporting may even understate the problem: There may be no way to measure accurately the increase in deaths associated with cocaine because of the inaccuracy of the reporting systems.

ONE CASE STUDY

For any research study of pregnant cocaine addicts, fetal heart rate tracing is an important tool. Such a fetal heart rate and uterine contraction pattern were obtained from a cocaine-addicted woman at URMC when she came in for delivery. When the baseline uterine activity began to increase, she underwent an emergency cesarean section and demonstrated a ruptured uterus. Fortunately, the baby was delivered safely and was put in the nursery. This kind of premature newborn appears in neonatology units all too often, in association with not only cocaine but also alcohol and heroin; this consequence of illicit drug use during pregnancy also consumes large numbers of health care dollars.

PSYCHOSOCIAL v. MEDICAL ISSUES

In many cases of drug abuse, the psychosocial needs of patients obscure the benefits of current medical resources. For example, the following scenario could happen in any labor and delivery. A 29-year-old pregnant woman had a history of alcohol, heroin, and cocaine abuse. She had no prenatal care except a visit in the first trimester. When she presented at 35 weeks to her family physician, the fetal ultrasound showed the baby was very small, with decreased amniotic fluid.

The patient left immediately and was lost to followup for 24 hours. She suddenly appeared in the URMC labor and delivery suite 8 centimeters dilated and quickly delivered a baby who was undergrown and who tested positive for cocaine and opioids. The mother missed her 6-week postpartum followup exam. Unfortunately, there is more to this story that illustrates why medical care failed. In 1990 she delivered at home a cocaine-positive baby who is now in foster care. The woman lives with an unemployed father, has only cereal and macaroni to eat, and admits to cocaine and heroin use five times a week and beer four times a week. She has been in rehab five times since 1990, the longest time for 10 months.

On February 16 her first ultrasound took place at Planned Parenthood, but she could not stay for the physical examination. A couple of months later, she appeared in the office intoxicated. She had not filled out the New York State Department of Social Services application. She applied for a new card and was referred to the Food Cupboard but did not go.

On July 14 the social worker's note said, "Still on cocaine, heroin, alcohol, marijuana. Refuses rehab." On July 15 the patient was seen (intoxicated) in the emergency room because she had shoved her arm through a window. On July 29 her social worker called her mother, but the phone had been disconnected. On July 30 extensive outreach efforts were made by both the New York State Department of Health and Baby Love (an outreach program), and the social worker's note for that date stated, "Still trying to assist."

On August 9 the young woman visited her family physician, and the next day she came into URMC in labor, 8 centimeters dilated, and delivered. Many resources were used to try to address this woman's concerns, but medical efforts were paralyzed by her psychosocial problems. Addressing the psychosocial problems of these patients is paramount because the best medical care will make no difference if it cannot be delivered.

PSYCHOSOCIAL ISSUES

The medical challenges of fetal monitoring, drug screening, and prenatal care have undergone many advances, but these issues may be only the tip of the iceberg. There are broader hurdles for these patients. Although the medical issues are important, the real targets should be the issues of poverty, rape, fear, distrust, and use of nicotine, alcohol, and other drugs. In addressing these issues, outreach programs can make contributions that complement available medical care. Health care practitioners need to understand how patients think: that they must hit bottom to seek help; that their self-esteem is low and is gone when they shoot up; that they hate the chaotic nature of clinics; and that they want to see the same person each time—a forceful example of the need for continuity of care.

According to patients, their patterns of living include timing their drug use around clinic visits, having no telephone and no transportation, and their greatest fear, losing custody of their children. No wonder they fear the involvement of researchers and health care workers in their care.

Obstetricians must learn how to utilize community resources when the answer to the question, "Do you use drugs?" is yes. Communities have many resources that could collaborate to help pregnant addicts—the prison system, settlement houses, residential and outpatient alcohol

and other drug treatment programs, schools, and sexually transmitted disease clinics.

Every community should develop a network that links obstetric activities to residential drug treatment programs and mental health programs that include intensive day treatment, outpatient care, and pediatric support. After delivery, the patient must be able to reenter the network educated about proper contraceptive care so that she can choose when to become pregnant. Much energy needs to go into outreach programs, because their participants serve as role models for other women, and the programs build trust, facilitate care, and follow through.

Health care providers need to be educated about the needs of these patients. Getting angry at them because they cannot follow the rules or becoming frustrated about having to fit them into clinic schedules is nonproductive. For patients who come in late and are told they have to reschedule, accountability is important but must be balanced with flexibility. A single mother who must travel across town with three children and make three bus transfers may arrive late for her clinic appointment. Clinics with strict rules that require her to reschedule serve no one's purpose. Drug screening is another issue. Although improved techniques for screening cocaine and other drugs exist, screening's most valuable function is that of challenging social workers to answer three questions: (1) Is the family functional and the home environment safe enough to let the baby return? (2) Is the newborn at risk from prenatal drug exposure? and (3) Can this woman enter drug treatment to improve her quality of living? When these questions are asked, screening is being done properly.

CONCLUSION

Some final questions that must be resolved are, Are we really in a drug war? Is drug abuse a crime, or is drug abuse a chronic relapsing disease like diabetes mellitus and chronic hypertension? As a result of progress that has been made in understanding drug abuse in pregnancy and the biology of drug abuse, more opportunities now exist to network within communities to bring together the fields of obstetrics, drug abuse prevention, and mental health. Through that kind of consortium, health care professionals can make a difference.

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