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Maine's High- Risk Infants and Maternal Health and Wellbeing: The Maine Infant Follow-Up Project

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The Maine Infant Follow-Up Project is a research-based effort to accelerate early identification of developmental risk for infants whose mothers use drugs or alcohol. These infants are at high risk for neurodevelopmental disorders, and early identification will enable early-early intervention. Targeted interventions will increase the chance for children to catch up developmentally during the period of most rapid brain growth in the first three years of life.

Maternal and child health is profoundly affected by Maine's regional landscape of intergenerational rural poverty and limited health care access. Economic and social disadvantage is all too common in Maine families and can derail the path to normal child development. Maine's rate of infant mortality in the first year is high, but similar to U.S. rural states, with leading causes being congenital anomalies, prematurity, sudden infant death syndrome (SIDS), and pregnancy and delivery complications.

According to the Web-based Injury Statistics Query and Reporting System (WISQARS) of the U.S. Centers for Disease Control and Prevention (www.cdc.gov/injury/wisqars/), SIDS in Maine represents 10 percent of all infant deaths compared to only 5.4 percent in the northeast region. Because of the known association of SIDS and prenatal alcohol and drug addiction (Hunt and Hauck 2006), Maine's elevated SIDS rate may reflect an acquired brain injury that is driven largely by poor maternal health, lifestyle, and economic adversity.

Although Maine has implemented policy changes to address the leading cause of infant death (i.e., congenital anomalies) with mandated statewide screening for a host of genetic and metabolic disorders at the time of birth, at present there is no public policy that mandates screening for long-term consequences of prenatal poverty-related risk factors (e.g., alcohol, tobacco, abuse of opiates and other substances, lack of prenatal care, malnutrition, and domestic abuse). Maine's spiraling need for services for developmental disabilities and special education (Maine Department of Education 2007) poses a crisis of care for early identification of developmental and behavioral disorders related to maternal addiction.

Regionally, northeastern Maine families show exceptionally low socioeconomic status (e.g., poor employment and education achievement; receipt of public assistance and Medicaid) that is correlated with alcohol, tobacco, and drug addiction (Hayes et al. 2002; Troese et al. 2008). During pregnancy and immediately after birth, unregulated drug and alcohol exposure of the developing child is probabilistically (dependent on genetic susceptibility, dose, and timing) related to neurological damage (e.g., poor respiratory and cardiac function associated with prematurity, and cognitive and motor deficits associated with oxygen deprivation), leading to developmental disabilities later in childhood.

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PRESCRIPTION OPIATE EPIDEMIC AND PRENATAL EXPOSURES

An increasingly large group of Maine infants are being exposed to prescription opiates as addiction reaches epidemic proportions statewide. Hospital admissions for prescription drug abuse increased 206 percent between 2004 and 2008 (Maine Department of Health and Human Services 2009). In the most recent National Survey on Drug Use and Health in Maine (2006–2007), 4.6 percent of those 12 or older (52,000 people) reported having used pain relievers nonmedically in the past year (Hughes, Sathe and Spagnola 2009). Young adults of childbearing age constitute the largest group of opiate-addicted patients, with 92 percent of the 500 women in treatment in Acadia Hospital's Narcotics Treatment Program (NTP) in Bangor being of childbearing age, and approximately 15 percent being pregnant at any given time.

The standard of care for pregnant women with opiate addiction is methadone maintenance through enrollment in a narcotics treatment program. Careful dosing of methadone matches the increasing metabolic demands of the growing fetus. In contrast, untreated opiate abuse (typically in a background of co-occurring maternal tobacco and alcohol abuse) exposes the fetus to repeated binge and withdrawal episodes responsible for high rates of in utero fetal death (Oei and Lui 2007). After birth, opiate-dependent infants are at high risk for numerous adverse effects, including a protracted withdrawal process. The severity of withdrawal is compounded by maternal psychiatric diagnosis requiring antidepressant and anti-anxiety

medications such as Prozac and benzodiazepines, which have their own withdrawal syndromes.

THE MAINE INFANT FOLLOW-UP PROJECT: EVALUATING RISK STATUS IN CHILDREN

The Maine Infant Follow-up Project is an effort to provide a longitudinal framework to accelerate the early identification of developmental risk to include the prenatal and early infancy period so that early-early intervention can be initiated. To date, our work has included more than 200 alcohol- and opiate-exposed infants and involves an interdisciplinary team with leadership from Dr. Mark Brown, chief of pediatrics at Eastern Maine Medical Center; Dr. Paul Tisher, former chief of psychiatry at Eastern Maine Medical Center and chief medical officer at Acadia Hospital; and the Maine Institute for Human Genetics and Health and University of Maine infant development team led by Marie Hayes. As part of our joint efforts to identify high-risk infants, we have characterized both prenatal substance exposure and environmental risk factors in different samples of northeastern Maine families. In the first study, disadvantaged women and their infants were studied from pregnancy onward with the goal of understanding the complex relationship between infant brain development, demographic risk, and prenatal exposure to alcohol and tobacco. In the second study, we again evaluated demographic and alcohol/tobacco risk in the context of opiate addiction, with an expanded suite of markers of brain development.

These two study cohorts were similarly exposed to rural poverty, as evidenced by their demographic characteristics. Groups were also similar on measures of psychological wellbeing, as indicated by scores on the Beck Depression Inventory, second edition (BDI-II), a screen for maternal depression.

In the first cohort, women were recruited from the Family Practice Clinic (FPC) of Eastern Maine Medical Center (EMMC), which serves low-income families from primarily Washington, Hancock, and Penobscot counties. Pregnant women were Caucasian (93 percent), single (64.7 percent), young (<26 years = 70.3 percent), unemployed (48 percent), and dependent on Medicaid (MaineCare) or had no health insurance (81.6 percent).

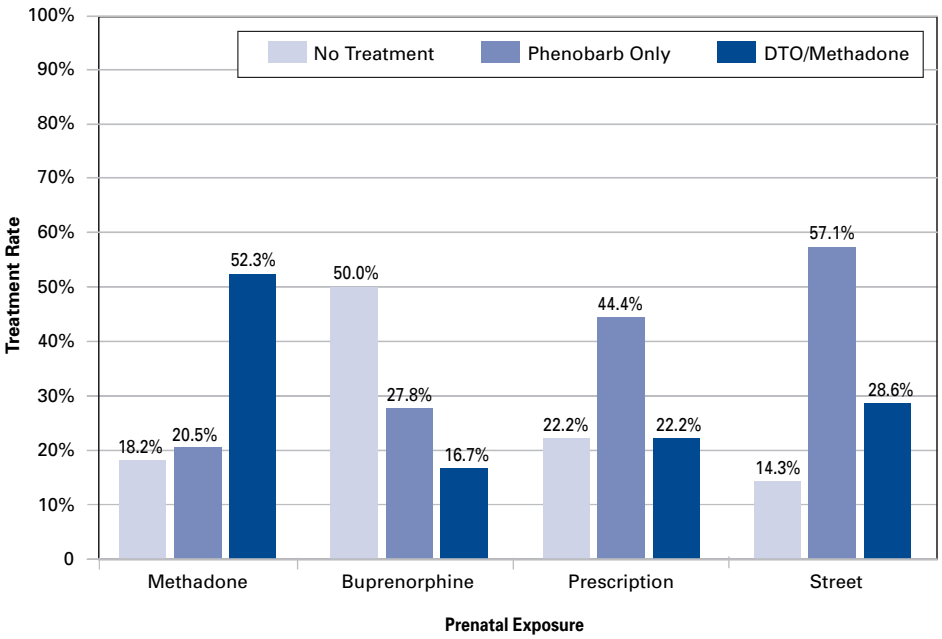
The second study was conducted in a cohort of families enrolled in the narcotics treatment program (NTP) at the Acadia Hospital in Bangor. The NTP serves primarily low-income, white families (97 percent Caucasian), ages 12 to 65, 47 percent female, from northeastern Maine. Mothers in this cohort were in recovery treatment for opiate addiction at Acadia NTP and were maintained on methadone during their pregnancies.

The groups did not differ statistically in tobacco use or pre-pregnancy or pregnancy estimates of alcohol use. Rates of tobacco and alcohol use in both samples were high, but similar to those of women of the same social class (SAMHSA 2008). The two study groups differed primarily in opiate and other illicit drug use pre-pregnancy, with the Acadia NTP group differing statistically in the use of opiates and other illicit drugs pre-pregnancy (opiates, marijuana, cocaine, and inhalants) from the FPC group. Hence, this comparison, allows us to study differences in outcomes for these infants that are unique to opiate and other polydrug exposure, given the samples are similar in alcohol, tobacco, and environmental risk factors.

Women had structured interviews during the third trimester with questions about their psychological health and the quantity, frequency, and timing of tobacco, alcohol and other substances both pre-pregnancy and during pregnancy, along with questions about tolerance and addiction to alcohol. These measures assess problem drinking and have been demonstrated in the literature to be valid indicators of the amount and severity of prenatal exposure (Jacobson and Jacobson 1996). Alcohol has well-established detrimental effects on brain development known as fetal alcohol syndrome/alcohol-related neurodevelopmental disorder (FAS/ARND) (May and Gossage 2001). Additionally, data from routine random urine analyses (UA), which screen for marijuana, methadone, oxycodone, other opiates, benzodiazepines, cocaine, and stimulant medications were collected. The most commonly detected illicit drug detected in UA screens was marijuana, followed by benzodiazepines and other opiates.

The first study found that infants whose mothers had high alcohol use patterns before and during pregnancy exhibited fragmented and unstable sleep along

FIGURE 1: **Treatment Rate for Neonatal Abstinence Syndrome, by Prenatal Exposure (November 2007–November 2008)**



with fewer normal sleep movements. Infants were sleep deprived, indicated by decreased alertness and increased irritability during the day. Tobacco smoking during pregnancy, present in 54 percent of the mothers, was associated with increased infant drowsiness associated with difficult transitions between sleeping and waking. Sleep deprivation represents an enormous risk to the developing infant; sleep integrity is critical in brain maturation and plasticity, but more importantly, sleep deprivation is associated with SIDS (for a more complete discussion, see Hayes et al. 2007).

In the second study, led by Dr. Brown, an interdisciplinary team of doctors, nurses and researchers evaluated the effects of different drug regimens on length of hospital stay, withdrawal severity, and infant irritability. Between 60 and 80 percent of opiate-exposed infants develop a condition called neonatal abstinence syndrome (NAS), a life-threatening collection of physiological symptoms of withdrawal (e.g., irritability, poor sleep and feeding, gastrointestinal distress, sweating and respiratory dysfunction) between 48 and 72 hours after birth. Sixty-six percent of infants in the study group experienced severe withdrawal symptoms that met criteria for NAS.

Figure 1 shows differences in withdrawal treatment based on type of addiction treatment during pregnancy. Infant outcome is measured in number of infants requiring no treatment, phenobarbitol, or opiate replacement, e.g., DTO (titrated dose of tincture of opium) or methadone. Mothers were treated with either methadone, bupenorphine (Subutex), prescription opiates, or no treatment (self-medication or using street drugs). While it appears that infants of mothers maintained on methadone were more likely to need more aggressive treatment for NAS (higher rates of DTO/methadone), it should be noted that methadone-treated mothers generally have more complex and longer-standing opiate addiction and other sociodemographic challenges than those on buprenorphine.

The differences seen in infant outcome based on treatment history highlight the importance of characterizing both the exposure history and the withdrawal profile of these high-risk infants. Managing and reducing the severity of NAS through new drug regimens have been implemented and have improved treatment and reduced the length of stay in the hospital. In the neonatal nursery at EMMC, mothers are strongly encouraged to breastfeed because of the demonstrated advantages for the high-risk infant's developing brain and the evidence from our group and others that withdrawal may be ameliorated by the trace amounts of opiates present in the breast milk (Abdel-Latif et al. 2006).

As part of the opiate study, the University of Maine team in collaboration with Dr. Krishnan has been examining opiate-exposed infants and matched controls for early cognitive function. Over the last decade, the behavioral and neural biomarkers to screen for cognitive developmental risk in the newborn using electroencephalography (EEG) cognitive testing have emerged (Molfese 2000). We found that newborn brain waves are predicted by prenatal exposure profiles:

women entering opiate-replacement treatment earlier have infants with better EEG associated with attention and memory function. In addition, withdrawal severity and drug replacement clearly impair the brain EEG response acutely, and perhaps for the long term, adding new urgency for improved pharmacological regimens for withdrawal treatment and prenatal maternal opiate management (Krishnan et al. 2008).

Because the population of opiate-addicted mothers is characterized as having poor access to health care resources, integrating child screens into narcotics treatment programs can activate mechanisms for early intervention. Under the leadership of Dr. Tisher, and in conjunction with the well child clinic at Acadia Hospital, the study team has established a follow-up clinic to evaluate long-term developmental consequences of NAS. Children are assessed at seven months using the Bayley Scales of Infant Development, which assesses motor, cognitive, and language development along with social and emotional functioning. In our current cohort, 50 percent of the children screened exhibit significant delays in motor function, an infancy marker of developmental delay. The relationship to withdrawal severity, prenatal methadone dose, and other prenatal and postnatal risk factors are suggestive but not yet clear.

Pushing back the window of child identification to the perinatal and early infancy period allows interventionists to take best advantage of the explosion of brain growth in the first three years.

Discussion

Clearly, early-early assessment is needed to improve pharmacological methods of prenatal methadone maintenance and safe withdrawal after birth, and to inform standards of care for these children who are at high risk of brain injury as they age. These current efforts to address the opiate crisis in the eastern Maine area have required tremendous focused adaptation from our existing health care infrastructure. The cutting-edge intervention system at Acadia Hospital is continuing to develop innovative care of the pregnant patient and her family in preparation for the birth of the opiate-exposed infant. There are prenatal parenting groups along with joint pediatric and NTP prenatal meetings with health care providers to prepare for hospitalization withdrawal complications. Additionally, the psychological adjustment to the birth of an infant, and often to first parenthood, is difficult for any mother, but is particularly difficult for a mother struggling with addiction recovery and economic stress. In addition to the typical challenges encountered by new parents, these families are also presented with the challenge of caring for a "temperamental" infant who suffers symptoms of withdrawal.

FUTURE DIRECTIONS AND POLICY IMPLICATIONS

Although modern medicine and intensive care interventions for newborns have revolutionized pediatric medicine, more efforts are needed to rehabilitate children suffering neurodevelopmental compromise. A large proportion of these complications are related to poor maternal prenatal health and substance abuse, often leading to ARND and in rare cases, FAS and NAS related to opiate withdrawal. Brain injury learning disabilities related to alcohol exposure show up in the child as social and cognitive processing deficits and attention-deficit hyperactivity disorder. In Maine, prescription opiate addiction has been added to the problem of alcohol abuse as a risk factor in early development. The brain developmental injury from these prenatal exposures conspires with environmental risk due to poverty to create more Maine children each year in need of special care, which if delayed until school-age, may lead to a lifetime of developmental disability.

High-risk infants are born to high-risk families living in high-risk environments. Often, developmental consequences show "sleeper" effects that emerge later in the toddler and childhood years; that is, apparently healthy infants may emerge as impaired at later points in their lives. Hence, environmental risk factors may

exacerbate preexisting prenatal risk factors when the child returns home.

The Maine Infant Follow-up Project is now working in collaboration with the national effort of the Sarah Jane Foundation called the "Pediatric Acquired Brain Injury [PABI] Plan" of intervention for brain injury during the early years (www.thebrainproject.org). Using cutting-edge assessment and treatment methods, we can identify at-risk children earlier. Pushing back the window of child identification to the perinatal and early infancy period allows interventionists to take best advantage of the explosion of brain growth in the first three years (Als et al. 2004).

It is well known that stimulating experiences and opportunities to practice new abilities in all developmental domains (e.g., cognitive, language, social, and motor) optimize brain development. Targeted early environmental enrichment that is maternal and family based is being implemented to increase the chance of developmental catch-up and recovery, led through an expansion of existing developmental care systems. This dynamic intervention model is based on new research in pediatrics, developmental psychology/psychiatry, and clinical neuroscience tied to the PABI national program for child brain injury. A statewide effort to improve early-early assessment and intervention promises a larger net for developmental catch-up, along with improved family and school support for caregivers working with children with brain injury.

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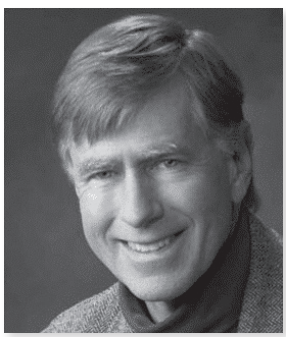
Beth A. Logan is a Ph.D. student in the developmental-clinical psychology program at the University of Maine. Her research examines the effects of methadone exposure on cognitive development. She is currently leading the Maine Infant Follow-up Project's early assessment and intervention program using psychology and clinical neuroscience methods in collaboration with the Acadia Hospital.

Marie J. Hayes is professor of psychology in the Department of Psychology and Graduate School of Biomedical Sciences at the University of Maine and senior scientist at the Maine Institute for Human Genetics and Health. Her research funded by the National Institutes of Health examines prenatal determinants of brain injury in high-risk infants and the application of biotechnology to detect early markers. She is interested in research that addresses maternal-child health in disadvantaged families.



Mark S. Brown, M.D., is chief of pediatrics and director of the Neonatal Intensive Care Unit and Nurseries at Eastern Maine Medical Center in Bangor, Maine. His commitment to continuous improvement to care has led to the HOME NOW Study, which was designed to ask whether there is a more effective treatment for infants with narcotic withdrawal.

Paul Tisher, M.D., held the position of vice president of medical affairs at Acadia Hospital and chief of psychiatry at Eastern Maine Medical Center, Bangor, Maine, from 1994 to May 2009. His earlier academic appointments included associate clinical professor in the Department of Psychiatry at Tufts University School of Medicine. He is currently working as a private consultant.

Jonathan A. Paul is a Ph.D. student in the University of Maine Graduate School of Biomedical Sciences, with a concentration in neuroscience. He is studying prenatal exposures and brain development, in particular the effects of prenatal methadone exposure. He has been using electroencephalography (EEG) methods to evaluate newborn cognitive deficits, along with sleep integrity and brain function in high-risk infants.

Ramesh Krishnan, M.D., is a neonatologist in the Pediatric Service at Eastern Maine Medical Center in Bangor, Maine, with a special interest in mechanical ventilation of the newborn lung and lung injury mechanisms. His other research interests include the neurocognitive and developmental effects on infants exposed to opiates in utero using event-related potential studies. He is the recipient of a Tufts University Charlton Grant award, which supports research projects likely to lead to funding from extramural sources, such as the National Institutes of Health and the National Science Foundation.