Addressing the impact of opioids on women and children

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Opioid overuse is an epidemic in the United States, with women and children bearing a significant share of its consequences. Women are more likely than men to have chronic pain, be prescribed prescription pain relievers, be given higher doses, and use these drugs for longer time periods. Women also become dependent on prescription pain relievers more quickly than men.[1] Gynecologic conditions such as endometriosis, fibroids, ovarian cysts, pelvic adhesions, and pelvic inflammatory disease are very common.[2,3] Women with these conditions often have chronic pain requiring lifelong management and are at risk for opioid use disorder (OUD).

Opioid use during pregnancy is a particular area of concern because it can lead to neonatal opioid withdrawal syndrome (NOWS), also known as neonatal abstinence syndrome. Across 30 states and the District of Columbia, rates of OUD diagnosed during pregnancy quadrupled from 1999 to 2014 (Figure).[4] Furthermore, rates of opioid prescription after delivery are high—one-quarter to one-third after vaginal delivery and over 80% following cesarean section—and a small proportion of these women become persistent users.[5,6]

In 2013 in Tennessee, 63 percent of cases of NOWS/neonatal abstinence syndrome were associated with maternal prescriptions for either opioid pain relievers or maintenance medications for OUD.[7] Between 2004 and 2014, among infants covered by Medicaid in 46 states, NOWS incidence increased 5-fold, to 14.4 per 1000 births.[8] Babies with NOWS occupy a substantial number of hospital beds, often in the neonatal intensive care unit. They require long initial hospital stays, intensive medication and management, ongoing social services, and sometimes foster care placement. In 2014, 82% of births affected by NOWS were covered by Medicaid at a cost of $462 million.[8]

Many newborns exposed to opioids in utero have difficulty eating and sleeping and are hard to console. Opioid-exposed babies may also be at higher risk of later developmental, behavioral, and educational[9] problems—and possible use of opioids and other substances during their own reproductive years. The stress of raising difficult-to-console babies in challenging social environments may cause mothers to relapse, putting a subsequent pregnancy in potential jeopardy. If left unchecked, these forces can drive intergenerational cycles of opioid use disorder. Finding the best ways to interrupt these cycles for mothers, babies, and families during several critical periods—before and during pregnancy, the newborn period, infancy, childhood, and adolescence—is crucial, yet solution-oriented research in these areas has been limited to date. There is also a need for research on the long-term consequences that these early adverse exposures have on the brain as it develops during childhood, adolescence, and adulthood.[9]

Two Populations of Research Focus: Infants and Women of Reproductive Age

Acting against neonatal opioid withdrawal syndrome

In 2017, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the Environmental influences on Child Health Outcomes (ECHO) program launched a series of studies to begin to address the specific medical and social needs of infants with NOWS. The project, called Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome, or ACT NOW, is part of the National Institutes of Health's HEAL (Helping to End Addiction Long-term) Initiative.[10] ACT NOW researchers are assessing current approaches to managing NOWS cases at more than 25 sites across the country. They are also developing common protocols for conducting large-scale clinical trials and cohort studies.

ACT NOW brings together NICHD's Neonatal Research Network, which has more than 30 years of experience designing and implementing clinical studies involving infants, and multiple components of ECHO, including the Institutional Development Award (IDeA) States Pediatric Clinical Trials Network. The IDeA States Pediatric Network focuses on rural and medically underserved communities in 17 states, many of which have been hit hard by the opioid epidemic.

After identifying gaps in knowledge in the treatment of infants affected by opioid exposure, NICHD and ECHO will initiate clinical trials and follow-up studies to provide evidence that will help to advance medical care for these newborns. These trials will likely focus on the following:

- Comparative effectiveness of different medication strategies, particularly how to wean babies off prescribed opioids for NOWS symptoms.
- Evaluation of comprehensive care quality improvement strategies that include pharmacologic and non-pharmacologic approaches (such as Eat, Sleep, and

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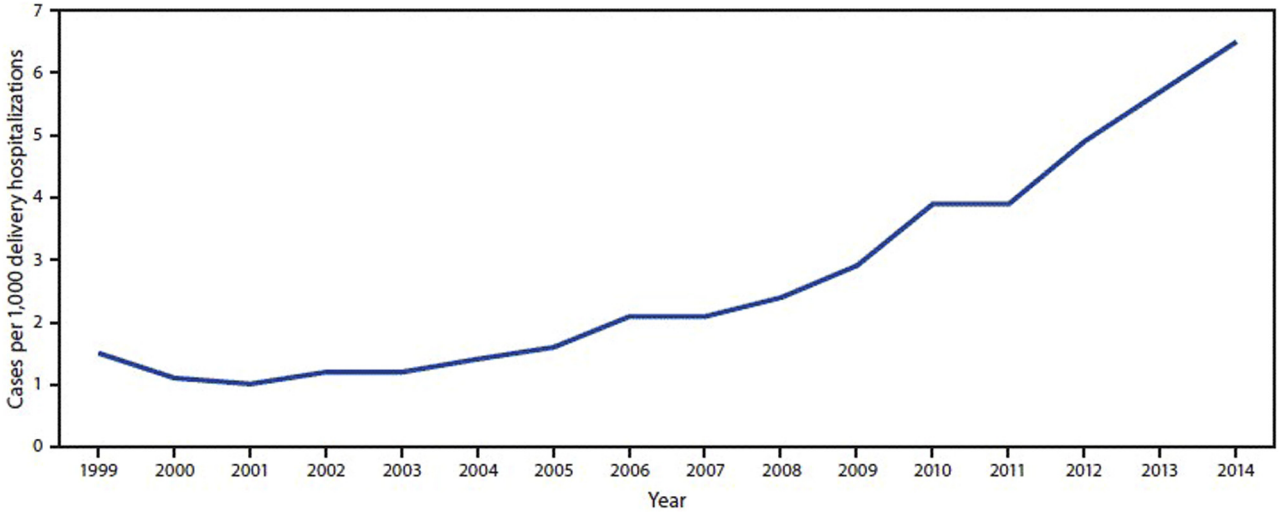
FIGURE
National prevalence of opioid use disorder per 1000 delivery hospitalizations in the United States, 1999–2014



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Console) combined with refined approaches to identifying babies with NOWS.

While the primary outcomes of such trials will likely be medication use and length of stay in the hospital, as part of interrupting the larger arc of maternal-child opioid use disorders, longer-term follow-up for children's brain development and family functioning is critical. The trials themselves may incorporate longer-term secondary outcomes. In addition, other opportunities may involve analyzing long-term data from existing maternal-child cohorts, such as those in the ECHO program, or establishing new cohorts that involve repeated developmental testing and neuroimaging of infants affected by NOWS.

New cohorts are especially needed to provide information on long-term effects of new synthetic opioids, as well as polysubstance use during pregnancy, including alcohol, tobacco, cannabis, and other prescription medications, which are often used in combination with opioids. Longitudinal studies are also necessary to explore the relationship between prenatal exposure and cognitive, behavioral, and social outcomes that may not manifest until later in childhood. These effects could increase the risk for future substance use and mental illness, thereby contributing to the intergenerational cycle of substance use.

Seeking solutions for women of reproductive age

Women of reproductive age, whether or not they become pregnant, represent another stage in the life course to interrupt cycles of opioid misuse.

To help address research gaps for opioid use disorder before and during pregnancy, NICHD, the National Institute on Drug Abuse, and others have solicited research projects related to the following topics:

- Clinical studies of medically supervised opioid withdrawal that evaluate potential outcomes such as maternal complications, loss to follow-up, overdose, relapse, fetal complications, pregnancy loss, and incidence and severity of NOWS.
- Pharmacokinetic and pharmacodynamic studies to optimize dose, duration, and frequency of medications used to treat opioid use disorder in pregnant and/or postpartum women.
- Observational cohort studies evaluating associations of medication-assisted opioid cessation (using methadone, buprenorphine, or naltrexone) with maternal, fetal, and neonatal outcomes.
- Pharmacogenomic and other studies of genetic and/or epigenetic factors associated with the effects of opioid use during pregnancy on fetal and neonatal outcomes.

In addition, women of reproductive age who have chronic and painful gynecologic conditions or have had gynecologic or pelvic surgery represent a population that can offer biological insights based on sex differences and critical early intervention points for maternal and child health.

Pelvic surgery, both obstetric and gynecologic, is a frequent opportunity for women of reproductive age to be exposed to narcotics, both during surgery and in the postoperative period. Cesarean delivery, for example, accounts for 32% of all births in the United States.[11] Recent data suggest that opioids prescribed after cesarean delivery generally exceed the amount consumed by a large margin, leading to substantial amounts of leftover medication, which could lead to nonmedical use.[12] In addition, postpartum women commonly receive similar amounts of opioids at hospital discharge regardless of their delivery method or measure of pain, pointing to a lack of standardization in prescribing patterns.[13]

Although limiting initial prescriptions for opioids is one approach for preventing the conversion to persistent users, the management of acute and chronic use requires other approaches, such as safe, nonaddictive, and effective pharmacologic and nonpharmacologic alternatives to opioid-based treatment. For example, the National Institutes of Health's HEAL initiative will support research to understand how chronic pain develops, identify new biomarkers for pain, and establish a clinical trials network to advance effective, nonaddictive pain medications.[14]

Research that explores how opioids affect women of reproductive age will serve as a powerful complement to the ACT NOW initiative. Together, these coordinated efforts promise to help turn the tide against the opioid crisis by providing the necessary evidence to improve care for women and children affected by these drugs. ■

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ABSTRACT

Addressing the impact of opioids on women and children

Women and children bear a substantial part of the burden of opioid overuse in the United States. Opioid use during pregnancy can lead to neonatal opioid withdrawal syndrome, and both the mothers and babies may be at higher risk of opioid use and its consequences later in the life course, setting up intergenerational cycles of opioid overuse. As part of the HEAL (Helping to End Addiction Long-term) Initiative of the National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the Environmental influences on Child Health Outcomes program are together launching observational and intervention research programs to interrupt these cycles, beginning with opportunities in pregnancy and the newborn period. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development has also launched programs to find alternatives to opioids for painful conditions in women of reproductive age, including a range of gynecologic conditions. These coordinated efforts promise to help turn the tide against the opioid crisis by providing the necessary evidence to improve care for women and children affected by these substances.

Key Words: children, opioids, women