Neonatal Opioid Withdrawal Syndrome: The NIH Response

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National Institutes of Health - Largest funder of biomedical research in the world

_Eunice Kennedy Shriver_ National Institute of Child Health and Human Development (NICHD) one of 27 Institutes and Centers
Background:

What is NOWs?

• Updated nomenclature for “Neonatal Abstinence Syndrome,” which was first identified in 1970s
• Refers to signs and symptoms in newborns prenatally exposed to opioids
• Characterized by irritability, tremors, feeding issues, vomiting, diarrhea, sweating, seizures, inability to be soothed
Opioid use has quadrupled over the last decade
259 million prescriptions for opioids in 2012
Every 3 minutes a woman seeks emergency care for prescription opioid misuse
Deaths involving synthetic opioids (mostly fentanyl) have increased from 3,000 to 20,000 in just three years
Health and Fiscal Impact of Opioid Use During Pregnancy

• On average, women take between 3 – 5 prescription medications during pregnancy

• Increased prevalence of opioid use during pregnancy ≥ 5 times increase in NOWs

• In 2012, nearly 22,000 infants were born with NOWs in U.S.

• Nationwide costs: $1.5 Billion in hospital charges for treating infants with NOWs

• In 2015, one Wisconsin county spent > $1 million (out of a $9 million budget) on child welfare placements, largely as a result of parental opioid addiction
Prevention of NOWs Starts With Prenatal Care

• Many women using opioids receive little or no prenatal care
  • Those who do are reluctant to disclose substance use
• Screen pregnant women with opioid use disorder at intervals throughout pregnancy to optimize care
• Medication-assisted therapy is the standard of care
  • Methadone treatment: improved compliance with obstetric care, higher birth weights, and lower preterm birth and infant mortality rates
  • Buprenorphine treatment: decreased risk of overdose and improved neonatal outcomes
• Interest has increased in medically supervised withdrawal, but unclear whether this approach safe for the pregnant woman and her fetus
Infants Exposed to Opioids

• Need to think about babies differently from adults
  • They generally do not die as a result of exposure
  • Most babies are born in the hospital and are resuscitated if they do not breathe
  • Not all newborns exposed to opioids develop significant signs of withdrawal right away

• In newborns prenatally exposed to methadone, signs of NOWs appear within 3-5 days of birth
  • Often after discharge from hospital

• Environmental factors (e.g., cigarette smoke) may increase incidence and severity of NOWs
What Can We Do For Infants With NOWs?

- Best managed in a calm environment
  - Where to treat?
    - Newborn intensive care unit, special setting, or home?
- Encourage breastfeeding
- Up to 80% require pharmacologic interventions (morphine or methadone)
  - When maximum dose reached, second line medication added
- Evaluation by social services
  - Can infant go home with mother or does infant require placement in foster home?
Breastfeeding

- Breastfeeding associated with decreased severity of NOWs, enhanced maternal-child bonding
- Breastfed infants less likely to need pharmacologic treatment compared to formula-fed infants
- Rates of breastfeeding are low – about half of women on methadone stop within 6 days of delivery
What is NIH Doing in Response to the Public Health Crisis of NOWs?
Building Expertise

• **NICHD** - Previously funded grants
  • Testing a drug treatment in pregnant women and their newborns to reduce the incidence or severity of NOWs (July 2012-May 2018)
  • Studies to determine more precise dosing of buprenorphine in pregnant women, given physiological changes (started in July 2015)

• **April 2016** - NICHD hosted a scientific workshop to identify research gaps for screening and management of opioid misuse and NOWs. Published in *Obstetrics and Gynecology* July 2017.

• **May 2016** - NIH/NIDA announced a new research effort to reduce the time it takes to improve or develop new medications to treat pain, addiction, and reverse overdoses.
Immediate Research Needs

• **Basic:** Identify neurodevelopmental consequences of *in utero* exposure to opioids;

• **Obstetric:** Determine optimal screening, treatment, and care during pregnancy;

• **Neonatal:** Develop a new screening tool for neurobehavioral assessment of newborn’s functioning, identify additional and optimal approaches to treatment;

• **Long-term:** Study outcomes of opioid exposure and treatment on brain development, cognitive function and overall child health.
New Funding Opportunity: Opioid Use Disorder in Pregnancy (RFA-HD-18-036)

Research Topics:

• Clinical studies of maternal medically-supervised opioid withdrawal examining maternal, fetal, and neonatal outcomes

• Pharmacokinetic and pharmacodynamic studies of medications used to treat opioid use disorder in pregnant and/or post-partum women

• Pharmacogenomic and other studies of genetic or epigenetic factors associated with the effects of opioid use during pregnancy on fetal and neonatal outcomes
ACT NOW: Advancing Clinical Trials in NOWs

• Initial funding received in August from Director Collins’ Discretionary Fund
• Partnership between NICHD/ECHO/NIDA
• FY 2018 Goals: (1) Develop a survey to obtain information on the sites, local practices, demographics, and volume of patients affected with NOWs
• (2) Develop and conduct an observational study to obtain prospective data to inform development of a clinical trial
• (3) Pilot a common protocol to generate evidence to inform best practice
The ACT NOW Partnership

Neonatal Research Network Centers (2016-2021)

- Started in 2016
- 17 sites, many are rural
- Sites overlap with areas of high prevalence of NOWs

IDeA States Pediatric Clinical Trials Network

- Started in 1986
- 15 sites, mainly urban
- Sites do not necessarily have high prevalence of NOWs

- Started in 2016
- 17 sites, many are rural
- Sites overlap with areas of high prevalence of NOWs
21st Century Cures Act: Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)

- NICHD is lead institute, first of three meetings held in August 2017
- Task Force report and recommendations due to HHS Secretary and Congress by September 2018
- Opportunities for scientific and public input on medications and other therapies used by pregnant and lactating women
- Prenatal and newborn effects included
- New attention to an under-studied issue
NICHD Pregnancy and Lactation Literature Analysis 2006-2017: Results for Pregnancy

- RCTs rare in almost all areas
- Exceptions:
  - Gestational diabetes
  - Hypertension
  - Preterm labor
  - Labor pain medication
  - Opioids and tobacco
Take Home Messages

• NOWs is a growing public health crisis
• Babies have different treatment needs than adults
• Most research at present focuses on short-term treatment
• Long-term effects of opioid exposure to developing brains are largely unknown
• Multi-disciplinary partnerships within and outside NIH are needed
• NIH’s role is to perform research that generates the evidence upon which professional groups can make recommendations
Questions?