Opioids in Pregnancy

Megan J. Huchko, MD, MPH
Associate Professor in
Obstetrics and Gynecology and Global Health
Duke University

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I have no financial or other conflicts of interest to declare

Women, Opioids and Pregnancy

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Learning Objectives

- Understand Epidemiology of Substance Use and Opioid Use in Pregnancy
- Learn effects of opiate use on mom, baby and pregnancy
- Options for treatment in pregnancy
- Understand how the current political climate impacts care for pregnant women who use opioids

1. What proportion of pregnant women use illicit substances?

A. 25%
B. 10%
C. 5%
D. <1%

Rates of Substance Use in Pregnancy

- Most common drugs in pregnant and non-pregnant women are tobacco and alcohol
- **11.4%** of non-pregnant women age 15-44 use illicit drugs
- **5.4%** of pregnant females report use of illicit drugs in past month
  - Many women who report are using more than one substance

- National Survey on Drug Use and Health, SAMHSA, 2014
- Pregnancy and Substance Use, Drug War Facts, 2015
Trends in Illicit Drug Use in Pregnancy

• Age: Younger women more likely to use substances in pregnancy
  – 15-17 yrs: 14.6%
  – 18-25 yrs: 8.6%
  – 26-44 yrs: 3.2%
• Duration of Pregnancy: reported drug use decreases with each trimester
• No identifiable relation to SES

• National Survey on Drug Use and Health, SAMHSA, 2014
• Pregnancy and Substance Use, Drug War Facts, 2015

Rates of Opioid Use in Pregnancy

• Difficult to find accurate statistics on use versus misuse
• One in three pregnant women will fill a prescription for opioid pain medication
• Approximately 0.2% pregnant women used heroin and 1% reported using opioid pain relievers non-medically in past month.1,2
  – Study showed 2.6% detection of opioids in urine2
• Between 2000 and 2009, number of pregnant women using or misusing prescription opioids increased from 1.2 to 5.6 per 1,000 births
  – NAS increased from 1.2 to 3.4 per 1,000 births
• 1% of CA-born neonates are exposed to opiates, majority from illicit use in pregnancy

1. SAMHSA, 2011-2012

Opioids and mechanism of action

• Opioids include
  – Opiates: Morphine, Codeine, Thebaine
  – Synthetics:
    • Oxycodone (OxyContin, Percocet)
    • Hydrocodone (Vicodin, Norco)
    • Hydromorphone (Dilaudid)
    • Heroin*
    • Methadone
    • Fentanyl
    • Nubain
    • Buprenorphine
• Taken as pills, suppositories or patches; smoked, inhaled, or injected (ASK!)
• Bind to receptors in the pleasure center in the brain (central tegmental area)
  – μ-euphoria, respiratory depression, constipation, sedation, miosis
  – κ-dysphoria, sedation, psychotomimetic
  – Δ – unknown
• Agonists release dopamine, serotonin and GABA/NMDA

Opioid Dependence vs Addiction

• Opioid use changes structure and metabolism of brain
• Physiologic dependence means steady dose necessary to achieve steady state
  – Increasing dose necessary for euphoria
• Once dependence occurs, a withdrawal syndrome occurs when drug not present
• Addiction to opioids characterized by:
  – Inability to abstain
  – Significant problems with interpersonal relationships
  – Impaired behavioral control
  – Cravings
  – Dysfunctional emotional response
• Often involves cycles of relapse and remission
• Addiction ≠ Dependency ≠ Abuse
Opiate Withdrawal

<table>
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<tr>
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<th>Late Withdrawal Symptoms &gt; 72 hrs</th>
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<td>• Diarrhea</td>
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<td>• Agitation</td>
<td>• Goosebumps</td>
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<td>• Difficulty sleeping</td>
<td>• Stomach cramps</td>
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<tr>
<td>• Anxiety</td>
<td>• Depression</td>
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<tr>
<td>• Nose running</td>
<td>• Drug cravings</td>
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<tr>
<td>• Sweats</td>
<td></td>
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<tr>
<td>• Tachycardia/palpitations</td>
<td></td>
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<tr>
<td>• Hypertension</td>
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<tr>
<td>• Fever</td>
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Withdrawal is a painful, but self-limited process for adults, but can cause permanent damage or death to the fetus.

Pregnancy and Opioid Use: A Complex Dynamic

- 86% of pregnant opioid-using women reported that their pregnancy was unplanned
- Pregnancy increases desire and ability to change drug use:
  - Motivational interviewing in pregnancy promotes abstinence
  - Compared to non-pregnant women, pregnant women are more likely to remain drug free (65.7% vs 27.7%)
  - 57% of pregnant women who use illicit substances reported abstaining during pregnancy

Issues facing substance-using women and their children

- Exposure to violence and trauma
- Generational drug use
- Lack of formal education
- Lack of job acquisition and maintenance skills
- Gender inequality/male-focused society
- Legal involvement
- Food insecurity and poor nutrition
- Multiple drug exposures
- Limited parenting skills and resources
- History of child abuse and neglect
- Co-morbid psychiatric issues
- Unstable housing
- Lack of positive and supportive relationships

These factors would influence maternal and child outcomes with or without drug use.

Opioid-Related Pregnancy Complications

- ? CHD
- Infections
  - Cellulitis/Abscess
  - Endocarditis
  - Osteomyelitis
  - Hepatitis/HIV
  - Septic thrombophlebitis
- IUGR/LBW
- Miscarriage
- Premature labor/PTB

Most of these are related to chronic, untreated heroin use.
Neonatal Abstinence Syndrome

- Results in approximately 50-90% of babies born to women using opioids in pregnancy
- Defined by alternations in the
  - Central nervous system
    - High-pitched crying, irritability
    - Exaggerated reflexes, tremors and tight muscles
    - Sleep disturbances
  - Autonomic nervous system
    - Sweating, fever, yawning and sneezes
  - Gastrointestinal distress
    - Poor feeding, vomiting and loose stools
  - Signs of respiratory distress
    - Nasal stuffiness and rapid breathing
- Can relate to fetal distress and death
- Maternal smoking increases risk for and severity of NAS
- Protocols vary, but mainstay is supportive care and morphine, some clonidine or phenobarb necessary
- Treatment necessary in approx 50% of NAS cases
- Public health and medical costs for NAS $70.6 to $112.6 million in US in 2009 alone

Screening for Opioid Use in Pregnancy

- ACOG recommends screening all pregnant women for substance use/abuse before pregnancy and in first trimester
- Be aware of signs and symptoms that may prompt re-screen
  - Late to care
  - Poor attendance at prenatal visits
  - Signs of sedation, withdrawal or intoxication
  - Physical signs of injection or complications
- Substance users come from all SES, race and age: the only way to identify appropriately is to ask ALL

How do you screen?

- Normalize the screening
  - Ask ALL pregnant women at their first visit
  - Explain that you ask to be able to provide the care they require for themselves and their fetuses
- Maintain caring and nonjudgmental approach
- Several screening tools work
  - 4 Ps (or 5 Ps)
  - CRAFFT
- Urine drug testing is an adjunct to detect or confirm use
  - Should only be used with patient’s consent and in compliance with state laws

Screening Tools

4 Ps
- Parents: Did any of your parents have a problem with alcohol or drug use?
- Partner: Does your partner have a problem with alcohol or drug use?
- Past: In the past, have you had difficulties in your life because of medications and drugs, including prescription medications?
- Pregnancy: In the last month, have you drunk any alcohol or used any drugs?

CRAFFT
- Have you ever ridden in a car driven by someone (including yourself) who was high or who had been using drugs?
- Do you ever use alcohol or drugs to relax, feel better about yourself or fit in?
- Do you ever use alcohol or drugs while you are by yourself or alone?
- Do you ever forget things you did while using alcohol or drugs?
- Do your family or friends every tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into trouble while you were using alcohol or drugs?
What is the recommended strategy for treating women who want to stop using opioids in pregnancy?

A. Monitored withdrawal with a goal toward abstinence
B. Medicated withdrawal to transition to abstinence
C. Medicated withdrawal to transition to lowest dose possible of maintenance therapy
D. Monitored transition to maintenance therapy avoiding withdrawal

Treatment of Opioid Use in Pregnancy

• Standard of care is TREATMENT, not withdrawal
  – Paradigm shift from lower possible dose to lowest doses necessary to prevent withdrawal
• Comprehensive opioid treatment that includes prenatal care reduces risk of obstetric complications
  
• Substance abuse treatment framework consists of 2 pillars
  – Medication-Assisted Treatment
    • Buprenorphine or Methadone
  – Therapy
    • Inpatient rehab center
    • Behavioral counseling
• Treatment should be done in collaboration with an addiction treatment specialist/program

Medication Maintenance vs Withdrawal in Pregnancy

Days Retained in Treatment

% Positive U Tox at Delivery
Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Hendrée E. Jones, Ph.D., Karol Kaltenbach, Ph.D., Sarah H. Heil, Ph.D., Susan M. Shor, M.D., Ph.D., Mara G. Coyle, M.D., Amelia M. Arria, Ph.D., Kevin E. O’Grady, Ph.D., Peter Selby, M.B., B.S., Peter R. Martin, M.D., and Gabriele Fischer, M.D.

- RCT to evaluate NAS in infants of 175 opiate dependent pregnant women maintained with buprenorphine vs methadone

NEJM, 2010
ACOG Treatment Recommendations

- **Buprenorphine has increasing amounts of data on use and safety**
  - In absence of long-term neurodevelopmental data, buprenorphine can be offered to patients in pregnancy
  - **Advantages**
    - Lower risk of overdose
    - Fewer drug interactions
    - Ability to be treated as an outpatient
    - Evidence of less severe NAS
  - **Disadvantages**
    - Reports of hepatic dysfunction
    - Lack of long-term data
    - Clinically important drop-out rate
    - Increased risk of diversion given outpt prescriptions
    - Potentially more difficult induction, could precipitate withdrawal
  - Recommend use of buprenorphine alone
  - Women should not transition between methadone and buprenorphine
  - Medically supervised withdrawal not recommended. If maintenance unavailable, or patient unwilling, 2nd trimester best timing

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methadone (n=21)</th>
<th>Buprenorphine (n=19)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Teratogenic defects — yes (%)</td>
<td>17 (77)</td>
<td>20 (105)</td>
<td>0.7 (0.3-1.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>MH peak score</td>
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<td>Infant’s head circumference — cm</td>
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<td>Weight at birth — g</td>
<td>2798.6±29.7</td>
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<tr>
<td>Length of birth — cm</td>
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<tr>
<td>Gestational age at delivery — wk</td>
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Treatment considerations

- May need:
  - Childcare arrangement during therapy or treatment
  - Transportation to and from outpatient treatment site
- Know state’s laws about drugs in pregnancy
- Long-term success
  - Help with housing after rehab
  - Programs that address stressors and coping
  - Education opportunities

Social work support essential!
How many states have laws that consider drug use in pregnancy “child abuse”?

A. 50  
B. 25  
C. 15  
D. 5

Current Legislation on Substance Use and Pregnancy

- Tennessee passed a law in 2014 making a misdemeanor criminal offense for babies to be born with detectable drugs in their system
  - Led to avoidance of prenatal care and few prosecutions
  - Not renewed July 2016
- 15 states consider drug use in pregnancy child abuse
- 18 states require health care professionals to report “suspected drug abuse” and 4 states require urine testing of suspected women
- 19 states have either created or funded drug treatment programs specifically targeted at pregnant women
- Obama Administration has supported treatment rather than criminalization
  - ACA supports treatment and intervention programs
- FDA issued a black-box warning for IR opioids 3/2016:
  - Include risk of NAS which may be “life-threatening”

ACOG on Opioids in Pregnancy

- ACOG response to Black-Box warning: Standard of care for women with an opioid-use disorder is medication assisted therapy
- Ob providers and patients should carefully weigh the risks and benefits when making decisions about initiating opioids for chronic pain
- Ob providers should not hesitate to offer opioids for appropriate indications in pregnant women based on a concern for NAS
- “Problem of drug and alcohol use in pregnancy is a health concern best addressed through education, prevention and community-based treatment, not through community drug laws or criminal prosecution.”

Caring for the Opioid Dependent Pregnant Woman

- Multidisciplinary teams essential for medical care and planning for delivery, parenting
- Elicit desires about pregnancy and childbearing
- Counsel regarding the pregnancy risks associated with drug use
- Identify and treat co-morbid conditions
- Maintain close communication with addiction medicine provider
- Work with pain team to ensure adequate pain relief in labor and post-partum/post-op
  - Treatment with maintenance opioids would not provide adequate pain relief
  - Women will require greater amounts of opioid-pain relief
- Pediatric staff should be notified
- Breastfeeding should be discussed and encouraged
- Remember post-partum birth control: discuss and decide during pregnancy
**Resources**

- ACOG Committee Opinion of Opioid Abuse, Dependence and Addiction in Pregnancy, Reaffirmed 2016
- ACOG Alcohol Abuse and Other Substance Use Disorders: Ethical Issues in Obstetric and Gynecologic Practice, June 2015
- ACOG Substance Abuse Reporting and Pregnancy: The Role of the Obstetrician-Gynecologist, Reaffirmed 2014
- Buprenorphine treatment:
  - [http://buprenorphine.samhsa.gov/bwns_locator](http://buprenorphine.samhsa.gov/bwns_locator)
- Methadone treatment:
  - [http://dpt2.samhsa.gov/treatment/directory.aspx](http://dpt2.samhsa.gov/treatment/directory.aspx)
- NPR on Opioid Use in Pregnancy:
- Resources for women with substance use disorders in pregnancy:

**What about a positive Utox?**

- Providers are unclear about
  - Their role in reporting?
  - The role of routine screening
- California does not require testing or reporting of suspected prenatal substance abuse
- While providers can make CPS referrals, social workers make final call at the time of delivery
- Drug testing can benefit women who are in treatment, or who have abstained from drugs in pregnancy
  - Early social work involvement can help navigate CPS

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**How Long is a Drug Detectable in Urine After Use?**

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<tr>
<th>Drug</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Amphetamines</td>
<td>24-72 hours</td>
</tr>
<tr>
<td>Alcohol</td>
<td>12-24 hours</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>10-30 days</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3-5 days</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2-4 days</td>
</tr>
<tr>
<td>Heroin</td>
<td>24-72 hours</td>
</tr>
<tr>
<td>Marijuana</td>
<td>3-30 days</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>3-10 days</td>
</tr>
<tr>
<td>Methadone</td>
<td>3 days</td>
</tr>
</tbody>
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**Opioid Replacement Medications: Buprenorphine**

- Schedule II opioid
- μ-receptor partial agonist
- Antagonist at the κ- and δ- receptors
- Half-life 24-60 hours
- 88% report concomitant drug use
- 50% occurrence of NAS
- Data in pregnancy limited, but buprenorphine considered safe
- Most treatment is done with Suboxone, combination of buprenorphine and naloxone
  - In pregnancy, buprenorphine ALONE is recommended to reduce risk of withdrawal
- Buprenorphine can be prescribed by accredited physicians who have undergone specific training

Pregnant women can with opioid disorders can be effectively treated with methadone or Buprenorphine. These medications should not be considered off-label for this indication.
Opioid Replacement Medications: Methadone

- Schedule II opioid
- Synthetically derived
- μ and δ receptor agonist
- Antagonist at the NMDA receptors
- Half-life estimated 24-36 hours
- Outpatient or inpatient initiation, followed by dosing at outpatient treatment center
- Pregnancy may impact dosing
- Inconsistent relationship between Methadone dose and NAS
- Methadone compatible with BF

Naltrexone

- Thebaine-derivative
- Schedule III opioid
- Pure antagonist at the μ-receptor with no agonist effects
- Single dose reaches plasma concentration in 1-2 hours with half life of 14 hrs
- Very limited research in pregnant women and breastfeeding
  - Available data and animal research suggest no adverse effect signals
- As a receptor antagonist, naltrexone doesn’t cause NAS
- Precludes use of opioids in pain relief and may alter pain threshold
  - Care team needs to be aware to tailor pain management strategy in delivery

Treatment for NAS

- Methadone associated NAS:
  - 55-90% of affected infants have signs of NAS
  - 60% require treatment
- NAS appears 45 to 72 hours after delivery
- NAS peaks 40 to 120 hours
- No standard treatment protocol, most common is morphine

Why the increase in opioid use in pregnancy?

- Overall increase in opioid use across the country in all demographics
  - Opioid prescription abuse is the fastest rising addiction and public health problem in the US
  - Over 2,000 deaths per week attributed to opioid abuse, mostly Oxycontin
- Increase in access to and delivery systems for opioids
- Pain became the “5th vital sign” early in the 21st century
- Florida did not have a prescription monitoring program, allowing “pill mills” to flourish as pain clinics
  - 41 million prescriptions for Oxycontin in Florida
  - 4 million for entire US
- Women more likely to abuse prescription drugs than men
**Impact of Opioid Use in Pregnancy**

- Data limited by confounding factors
- Increase in the risk of birth defects?
  - Conflicting studies suggest increase in CHD
  - Methodologic issues
- Need for increased or alternative pain regimens due to change in pain tolerance
- Can inhibit ability to attend prenatal care and affect relationship with providers

Zierler, NEJM, 1985, Bracken NEJM, 1986
Broussar, Am J Obstet Gynecol 2011

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**Treatment vs Detoxification**

- Buprenorphine or methadone can be used as
  - Maintenance therapy: treatment for an indefinite period of time by maintaining steady states of opioid levels to reduce craving and withdrawal
  - Medication-Assisted withdrawal: consecutive reduction in the dose of medication to provide a smooth transition from illicit opioid use to a medication-free state
- Medication-> withdrawal has high attrition rate and rapid return to illicit opioid use
- Medication maintenance allows for patient retention and reduces substance use rates

Pregnant women seeking treatment should undergo a transition to maintenance therapy. Abrupt withdrawal from opioids can be life-threatening to the fetus.

WHO Guidelines, 2014

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**Long term outcomes for drug-exposed children**

- No consistent evidence for long-term adverse events associated with NAS
- No significant impairments for cognitive, psychomotor or observed behavioral outcomes for infants or pre-school aged children exposed in-utero to methadone maintenance
- ACOG: Does not appear to pose permanent risks to neonate

Baldacchino et al, BMC Psychiatry 2014
ACOG, 2016