OPIOID USE AND OPIOID MISUSE IN PREGNANCY- CONSIDERATIONS FOR MANAGEMENT

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Professor University of Tennessee
OBJECTIVES

• At the end of this lecture, the participant should be to
  • Identify the need for identifying patients with opiate use disorder
  • Discuss the need for comprehensive care for patients with opioid use disorder
  • Implement a management plan for caring for women with opioid use disorder
THE PROBLEM

• Illicit drug use in the United States is at its highest point in a decade
• Women comprise 30% of the addicted population
  • Majority are of childbearing age
• Substance misuse and overdose deaths have become a public health crisis
• In 2012, rate of use of illicit substances during pregnancy was 5.9%
• In 2010, the rate was noted at 4.4%
• Note this does not include alcohol, prescription drugs nor tobacco!!
OPIOID USE DISORDER
THE PROBLEM

• In 2012, US health care providers wrote more than 259 million prescriptions for opioids
  • Twice the number of people in the US
• Rates of admission to treatment programs for opioid misuse disorder have more than quadrupled in 10 years
• Rate of death associated with opiates has increased 400%
• Neonatal abstinence has increased 4x in 10 years
  • Associated with an over 1.5 billion dollars in health care charges
• Has become a major risk factor for maternal mortality
OVERDOSE DEATH RATES IN AMERICA

All underlying causes of death*

*Includes deaths from unintentional drug poisoning, suicide drug poisoning, homicide drug poisoning or drug poisoning of undetermined intent.

SOURCE: Wonder.cdc.gov

BUSINESS INSIDER
Figure 14. Leading Immediate Causes of Pregnancy-Associated, but Not Related Deaths, Tennessee, 2017

- Overdose: 13 deaths
- Motor Vehicle Accident: 13 deaths
- Violence: 8 deaths
- Underlying Substance Use: 6 deaths
- Other Medical Related Diagnosis: 3 deaths
- Cardiac Related: 3 deaths
- Cancer: 3 deaths

Total: 49 deaths
Figure 6: Contributing Factors for All Pregnancy-Associated Deaths, Tennessee, 2017

Data Source: Tennessee Department of Health, Division of Family Health and Wellness, Maternal Mortality Review Program.
RISK FACTORS

• History of previous substance use
• History of mental illness
• History of sexual abuse
• Lack of knowledge regarding risk
• Easy access
In 19th century cocaine and morphine isolated, cigarette rolling machines invented

Opium was marketed frequently to women for the treatment of menstrual disorders

1st cocaine epidemic 1885-1920---father of modern surgery—Halstead was addicted to cocaine. Coca-Cola was initially contained the drug

1906 Pure Food Drug Act required patent medicine be labeled
1919 Supreme Court ruled illegal maintain addict (indefinite prescriptions)

1960 Methadone maintenance introduced

1980s Crack epidemic

1988 Anti Drug Abuse Act: targeted causal user and dealer, shift → enforcement vs. treatment (warning pregnant women)

2000 Opioid Epidemic
A maladaptive pattern of substance use leading to clinically significant impairment or distress manifested by 3 or more following 12 month period

1. Tolerance
2. Withdrawal
3. Larger amounts of substance
4. Persistent desire
5. Time mismanagement
6. Give up important activities
7. Persistent use

Mild 2-3; Moderate 4-6; Severe 7-11

DSM V 2013 APA
CASE 1

- KT presents to your office for her first prenatal visit. She is married. She and her partner are excited about this pregnancy. KT is a college graduate and is currently in graduate school. Based on ACOG recommendations, you should:
  - Place her in a low risk category
  - Tell her that you do not think that she uses substances
  - Screen her for substance use at this visit
  - Wait until another time, screening takes too long
• Early universal screening and referral for treatment for pregnant women with opioid use and opioid use disorder improve maternal and infant outcomes
SCREENING

- CRAFFT
- PASS
- NIDA Quick Screen
CRAFFT (FOR WOMEN 26 AND UNDER)

• **C** - Have you ever ridden in a **CAR** driven by someone (including yourself) who was high or had been using alcohol or drugs?

• **R** - Do you ever use alcohol or drugs to **RELAX**, feel better about yourself or fit in?

• **A** - Do you ever use alcohol or drugs while you are by yourself or **ALONE**?

• **F** - Do you ever **FORGET** things you did while using alcohol or drugs?

• **F** - Do your **FAMILY** or **friends** ever tell you that you should cut down on your drinking or drug use?

• **T** - Have you ever gotten in **TROUBLE** while you were using alcohol or drugs?
4P’S

• Have you every used substances during pregnancy?
• Have you had a problem with substances in the past?
• Does your partner have a problem with drugs or alcohol?
• Do you consider one of your parents to be an addict or alcoholic?
**NIDA QUICK SCREEN**

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Once or Twice</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily or Almost Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2. <strong>In the past 3 months</strong>, how often have you used (insert name of drug)?</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Q3. <strong>In the past 3 months</strong>, how often have you had a strong desire or urge to use (insert name of drug)?</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Q4. <strong>In the past 3 months</strong>, how often has your use of (insert name of drug) led to health, social, legal or financial problems?</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Q5. <strong>In the past 3 months</strong>, how often have you failed to do what was normally expected of you because of your use of (insert name of drug)?</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

Ask Questions 6 & 7 for all substances **ever used** (i.e., those mentioned in Question 1):

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>YES, but not in the last 3 months</th>
<th>YES, in the past three months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q6. Has a friend or relative or anyone else ever expressed concern about your use of (insert name of drug)?</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Q7. Have you ever tried and failed to control, cut down, or stop using (insert name of drug)?</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

**Instructions:** Ask Question 8 if patient mentions ANY drug that might be injected, including those that might be listed in the ‘Other’ category (e.g., steroids). Circle appropriate response.

<table>
<thead>
<tr>
<th>Question</th>
<th>No, never</th>
<th>YES, but not in the last 3 months</th>
<th>YES, in the past 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8. Have you ever used any drug (including steroids) by injection?</td>
<td>No, never</td>
<td>Yes, but not in the last 3 months</td>
<td>Yes, in the past 3 months</td>
</tr>
</tbody>
</table>

* Indicate you are referring to non-medical use only.

**Substance Involvement (SI) Score**

(Add all numbers circled in the questions)
NIDA QUICK SCREEN

• Step 1
  • Ask patient about drug use—the online screen

• Step 2
  • Begin NIDA-Modified ASSIST

• Step 3
  • Determine the risk level
  Conduct a brief intervention

• Step 4
  • Advise, Assist and Arrange
WHAT ABOUT URINE DRUG SCREEN

- Patient consent should be obtained
  - Universal screening should be implemented
  - Remember urine testing only assesses for recent substances
- Social services and assistance should be available
- Urine toxicology may not detect
  - Synthetic opioids
  - Some benzodiazepines
  - Designer drugs
- False-positives
  - Labetalol
  - Methyl-dopa
  - Poppy seeds
JL is a 32 year old G4P2012 who presents at 15 weeks gestation for routine prenatal care. Upon taking your history, the patient reports that she has “pain” and takes 20 mg of oxycodone 3 times per day. She used to have a prescription, but she recently has been getting her medications from her friends because she has had some withdrawal. You inform the patient

- That would will continue writing for her medications
- You suggest opiate replacement therapy
- Tell her that she keep taking her friends medication
- Delay urine drug screening as it will be positive
You should suggest initiating opiate replacement therapy
OPIATES

Natural alkaloids
- morphine
- codeine
- thebaine

Semi-synthetics
- heroin
- oxycodone
- hydrocodone
- buprenorphine
- naloxone
OPIOIDS

Pure agonists
- morphine
- oxycodone
- fentanyl

Antagonists
- naltrexone
- naloxone

Mixed agonists/antagonists
- buprenorphine
- nalbuphine
- tramadol

Others
Partial vs Full Opiate Mu Agonist

- **Full Agonist** (e.g., methadone)
- **Partial Agonist** (e.g., buprenorphine)

Opiate Effect vs Dose of Opiate

- Death
## Classification of Opiate Receptors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mu (µ)</th>
<th>Delta (δ)</th>
<th>Kappa (κ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Ag</td>
<td>Ag</td>
<td>Ag</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Ag</td>
<td>Ag</td>
<td>Ag</td>
</tr>
<tr>
<td>Methadone</td>
<td>Ag</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine HCl</td>
<td>pAg</td>
<td></td>
<td>Ag</td>
</tr>
<tr>
<td>Butorphanol tartrate</td>
<td>pAg</td>
<td></td>
<td>Ag</td>
</tr>
<tr>
<td>Nalbuphine HCl</td>
<td>pAg</td>
<td></td>
<td>Ag</td>
</tr>
<tr>
<td>Buprenorphine HCl</td>
<td>pAg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone HCl</td>
<td>Ant</td>
<td>Ant</td>
<td>Ant</td>
</tr>
</tbody>
</table>
THE HIGH:
Morphine’s activation of the opioid receptor in neurons of the nucleus accumbens in the brain 1 reigns in the release of the neurotransmitter γ-aminobutyric acid (GABA) 2. This drop in GABA causes a neighboring cell to expel dopamine 3, which in turn elicits the euphoria associated with opioids.
GENETICS OF OPIATE USE

Diagram showing the genetics of opiate use, with pathways for methadone, heroin/opioid addiction, Naltrexone + Nalmefene, alcohol addiction, and the receptors NMDA-r, N/OFQ-r, MOP-r, and KOP-r. The diagram also indicates the use of antagonists (red lines), agonists (black lines), and partial agonists (dashed lines) for Buprenorphine in heroin/opioid addiction.
Methadone

- synthetic opioid blocks effect of the opioid
- long half life allows daily dosing
- no euphoria, no interference with daily activity
METHADONE TREATMENT PROGRAMS

- 30 years of experience
- Advantages
  - Oral administration
  - Known dose and purity
  - Safe and steady availability
  - Not associated with birth defects
- Disadvantage: Neonatal abstinence syndrome
METHADONE PERINATAL EFFECTS

- **Pregnancy**
  1. continuation of normal daily activity
  2. decrease in associated maternal morbidity

- **Neonatal Abstinence Syndrome**
  1. occurs on day 2 - 3 up to a week
  2. similar to heroin withdrawal syndrome
  3. Naloxone (narcan) contraindicated severe withdrawal
THE USE OF BUPRENORPHINE (SUBUTEX) IN PREGNANCY

• Buprenorphine, more popularly known by the brand names Subutex and Suboxone is another heroin substitute. It is another opiate which was actually first marketed as a pain-killer in the 1980s with brand names Tamgesic (oral) and Buprenex (injectable).

• Buprenorphine has been demonstrated to gradually reduce the craving for opiates such as heroin and also reduce severity of withdrawal symptoms. As such, it is another drug now used as a heroin substitute.

BUPRENORPHINE PHARMACOLOGY

- Partial agonist at mu receptor
- High affinity for mu receptor
- Can displace full opiate agonist such as heroin or methadone
  - Displacement of heroin or methadone by buprenorphine can produce opiate withdrawal symptoms
BUPRENORPHINE
PHARMACOLOGY

- Antagonist at kappa receptor
- Poor bio-availability taken orally (extensive first pass metabolism)
- Much more bio-available from sublingual mucosa (Peak 2-3 hours following sublingual dose)
- Dosage usually 8mg to 16 mg daily, some patients may require up to 32 mg
BUPRENORPHINE VERSUS METHADONE

• 515 neonates exposed to buprenorphine
• 885 neonates exposed to methadone
  • Meta-analysis of 12 studies
  • Outcomes
    • Neonates exposed to buprenorphine had less NAS with higher birthweight and gestational age
    • Less relapse to other opiates
      • Brogley et al, Amer J of Epid 2014 Oct 1;180(7):673-86
BUPRENORPHINE VERSUS METHADONE

- Moderately strong evidence indicates lower risk of preterm birth, greater birth weight and larger head circumference with buprenorphine treatment of maternal opioid use disorder during pregnancy compared with methadone treatment, and no greater harms.
BUPRENORPHINE VERSUS METHADONE

• If a patient is stable on methadone or unable to comply with doses, methadone may be a better option
  • Longer half-life
  • Not all women will require dosage increases in pregnancy
  • Lower doses are not associated with a decrease in NAS
CASE 3

TP is a 33 year old G1 who presents for routine prenatal care at 18 weeks. She is in a substance program and is currently on Suboxone (buprenorphine and naloxone). You inform the patient that she should:

• Stop her medication and switch to buprenorphine
• Continue her current dose
• Stop all medications because she is pregnant
• The patient should continue her current medications. Naloxone is not orally active.

• The naloxone reduces the risk of IV use and drug diversion

• Data suggest that Suboxone is not associated with adverse fetal defects
CASE 4

• BB presents to our ED at 17 weeks gestation in active opiate withdrawal. She reports that she was taking Roxies on the street but she has not taken any medication in the last 2 days. Her history is remarkable for a history of endocarditis due to IV substance use. What is your next step?
  • Tell the ED she is only 17 weeks gestation and they should not call you
  • Tell them that since she has not taken medication for several days, she doesn’t need medications anymore
  • Determine the patient’s level of withdrawal and begin opiate replacement therapy
  • Try to wait until the other team arrives, after all you only have 45 minutes left on call
ANSWER

• Determine the level of the patient’s withdrawal and initiate opiate replacement therapy
OPIATE WITHDRAWAL: RECOGNIZING THE SIGNS

• Early signs
  • Irritability
  • Agitation
  • Anxiety
  • Aches and pains
  • Yawning
  • Increased tear production / watery eyes
  • Runny nose
  • Inability to fall asleep or to stay asleep
OPIATE WITHDRAWAL: RECOGNIZING THE SIGNS

• Later signs
  • Abdominal cramping
  • Diarrhea
  • Nausea
  • Vomiting
  • Dilated pupils
  • Tachycardia
  • Hypertension
  • Goose bumps, feeling cold
**CALCULATING THE COWS SCORE**

**COWS**  
Clinical Opiate Withdrawal Scale

<table>
<thead>
<tr>
<th>Resting Pulse Rate:</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>GI Upset over last 1/2 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured after patient is sitting or lying for one minute</td>
<td>Pulse rate 80 or below</td>
<td>Pulse rate 81-100</td>
<td>Pulse rate 101-120</td>
<td>Pulse rate greater than 120</td>
<td>No GI symptoms</td>
<td>Stomach cramps</td>
</tr>
</tbody>
</table>

**Swelling:** over past 1/2 hour not accounted for by room temperature or patient activity.  
0 | No report of chill or flushing |
1 | Subjective report of chill or flushing |
2 | Flushed or observable moisture on face |
3 | Heads of sweating on brow or face |
4 | Sweating streaming off face |
| Tremor observation of outstretched hands |
0 | No tremor |
1 | Tremor can be felt, but not observed |
2 | Slight tremor observable |
3 | Gross tremor or muscle twitching |

**Restlessness Observation during assessment**  
0 | Able to sit still |
1 | Reports difficulty sitting still, but is able to do so |
2 | Frequent shifting or executives movements of legs/arms |
3 | Unable to sit still for more than a few seconds |

**Pupil size**  
0 | Pupils pinned or normal size for room light |
1 | Pupils possibly larger than normal for room light |
2 | Pupils moderately dilated |
3 | Pupils so dilated that only the rim of the iris is visible |
| Anxiety or irritability |
0 | None |
1 | Patient reports increasing irritability or anxiousness |
2 | Patient obviously irritable anxious |
3 | Patient is irritable or anxious that participation in the assessment is difficult |

**Bone or Joint ache:** If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored.  
0 | Not present |
1 | Mild diffuse discomfort |
2 | Patient reports severe diffuse aching of joints/muscles |
3 | Patient is rubbing joints or muscles and is unable to sit still because of discomfort |
| Gooseflesh skin |
0 | Skin is smooth |
1 | Pleroration of skin can be felt or hairs standing up on arms |
2 | Prominent pilaration |

**Ruddy nose or tearing:** Not accounted for by cold symptoms or allergies  
0 | Not present |
1 | Nasal stuffiness or unusually moist eyes |
2 | Nose running or tearing |
3 | Nose constantly running or tears streaming down cheeks |

Score: 5-12 mild; 13-24 moderate; 25-36 moderately severe; more than 36 = severe withdrawal

Can start therapy at a score of 8 or greater
CASE 5

• JY presents at 12 weeks gestation. She has been on maintenance therapy for a while and is currently on 4 mg of buprenorphine. The patient wants to stop this pregnancy. You inform the patient
  • That the scientific evidence suggest that stopping opiates in pregnancy results in fetal stillbirth and it should not be done
  • That the scientific evidence suggest that she may be more likely to relapse but that if she is motivated some data suggest that it can be successfully undertaken
  • You are not sure of the answer
That the scientific evidence suggest that she may be more likely to relapse but that if she is motivated some data suggest that it can be successfully undertaken.
Detoxification from opiate drugs during pregnancy

Jennifer Bell, MD; Craig V. Towers, MD; Mark D. Hennessy, MD; Callie Heitzman, RN; Barbara Smith; Katie Chattin

Results
Over 5.5 years, 301 opiate-addicted pregnant patients were fully detoxified during pregnancy with no adverse fetal outcomes related to detoxification identified. There were 94 patients who delivered newborns treated for neonatal abstinence syndrome (31%). There was an 18.5% rate of neonatal abstinence syndrome in the 108 acutely detoxified while incarcerated, a 17.4% rate of neonatal abstinence syndrome in the 23 who had inpatient detoxification with intense outpatient follow-up management, a 17.2% rate of neonatal abstinence syndrome in the 93 who went through slow outpatient buprenorphine detoxification, but a 70.1% rate of neonatal abstinence syndrome in the 77 who had inpatient detoxification without intense outpatient follow-up management.

Conclusion
With these data and other published studies, more than 600 patients have been reported to detoxify from opiates during pregnancy with no report of fetal harm related to the process. These data highly suggest that detoxification of opiate-addicted pregnant patients is not harmful. The rate of neonatal abstinence syndrome is high but primarily when no continued long-term follow-up occurs. Once a patient is drug free, intense behavioral health follow-up is needed for continued success.
Evidence does not support detoxification as a recommended treatment intervention as a result of low detoxification completion rates, high rates of relapse, and limited data regarding the effect of detoxification on maternal and neonatal outcomes beyond delivery.

- Teplan et al, Obstet Gynecol 2018
NALTREXONE

- Non-selective opioid antagonist
- Blocks the euphoria from opiates
- Limited data in pregnancy
- Concern over fetal defects
- Randomized controlled trials are needed
MEDICAL COMPLICATIONS

• Hepatitis C
  • All pregnant women should be tested for Hepatitis C
  • HCV RNA and routine liver functions are recommended at the initiation of prenatal care for all HCV positive women to assess risks
  • Patients with pruritis or jaundice should be considered to have cholestatic jaundice of pregnancy
  • HCV-infected women with cirrhosis should be counseled regarding a poor outcome
  • Hepatotoxic drugs should be avoided
  • Breastfeeding is not contraindicated
  • Assess postpartum for spontaneous viral clearance
    • ISDA, 2019
Endocarditis

- Infective endocarditis is increasing in incidence due to the IV drug use epidemic
- Can be life-threatening>>mortality as high as 11%
- Risk factors
  - Previous valvular disease
  - IV drug use
- Predictors of a poor outcome
  - Thrombocytopenia
  - Sinus tachycardia
  - Elevated creatinine
- Valvular damage may persist after episode
ANTEPARTUM MANAGEMENT

• Screening for STI’Cs
  • Hepatitis C
  • Hepatitis B
    • Treatment in the 3rd trimester for those who are positive
    • Vaccination during pregnancy for whose at high risk
  • HIV
  • TB
  • GC/Chlamydia

• Screening for mental health issues
  • Depression

• Screening for Intimate Partner Violence

• Counseling regarding smoking cessation
  • Reduces risk of NAS
OPIATE USE

- Serial ultrasounds for fetal growth
- Twice weekly antenatal testing at 32 weeks gestation
  - FHR baseline and variability may be reduced in patients who have taken medications
  - BPP may take longer but remain unchanged
INTRAPARTUM

- Epidural anesthesia is recommended
- Avoid partial opiate antagonist (Stadol, Nubain)
  - These medications can cause withdrawal
• Breastfeeding is strongly encouraged
  • Reduced neonatal abstinence syndrome
• Pain needs in this population may be increased
  • Do not withhold pain medications—patients may need more
  • One study demonstrated that women who took buprenorphine needed 47% more opioid analgesia
• Consider non-steroidal and acetomeniphine use
• Social services consultation
  • Follow up with patient after delivery to make sure patient stays in treatment
POSTPARTUM PREVENTION

• Providers over-prescribe the number of opiates required in the postpartum period
  • 246 patients
    • 83% of patients use opioids a mean of 8 days postpartum C/S
    • 75% of patients had unused tablets
    • 63% stored them in an unlocked location
    • 95% had not disposed on the medication
      • Osmoundson, Obstet Gynecol 2017
      • Batemen, Obstet Gynecol 2017
POSTPARTUM

• Contraception
  • Unintended pregnancy rates in patients with substance use disorders is as high as 80%
  • Consider LARC
    • Address with patient prior to delivery
NEONATAL ABSTINENCE SYNDROME

• NAS occurs in 30-80% of infants born to women taking opiate replacement therapy
• The use of other substances, nicotine, benzodiazepines and SSRI’s may increase the incidence and severity
• Studies have not found significant differences in cognitive development
STRATEGIES TO IMPROVE MANAGEMENT

• Change perceptions of opioid and substance use disorder by using common language
  • Given the severity of the epidemic, we need to reduce the stigma associated with this disease

• Develop and offer education to health care providers in caring for patients with opioid use disorder

• Create better engagement and communication between providers with the continuum of care and across service areas, including the justice system
  • Resources are often in multiple places.

• Enhance patient and family engagement

NYS Health Foundation, 2017
Substance misuse is a treatable disease
No single treatment is appropriate for all individuals
Recovery from drug addiction is a long term process (relapses)
Effectiveness is dependent on remaining in treatment
SELECTED REFERENCES

- ACOG Committee Opinion, Number 117. Opiate Use and Disorder in pregnancy. August 2017