PCSS MAT TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Opioid Dependence in Pregnancy: Clinical Challenges

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Jeffrey DeVido, Disclosures

- Dr. DeVido has no conflicts of interests or disclosures relevant to the content of this presentation.

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Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Discuss the **epidemiology** of substance use disorders (opioid use disorders in particular) in pregnant women
  - Understand both the maternal and fetal/infant **risks** of opioid use disorders in pregnancy
  - Discuss the range of **screening** approaches to opioid use disorders in pregnancy
  - Understand **mandatory reporting** issues
  - Understand the various **medication-assisted-treatment** (MAT) options for opioid dependent pregnant women including:
    - Naltrexone, Methadone, and buprenorphine
  - Discuss **behavioral** treatment options for management of opioid use disorders in pregnant women

Epidemiology: Trends in Substance Use and Women

- Prevalence of substance use disorders (SUDs) in men remains higher than in women
- However, this gap is steadily closing (Keyes 2008; Steingrimsson 2012)
- 42% of 41.5 million individuals who reported using illicit drugs in the past year were women

  (2012 National Survey on Drug Use and Health (NSDUH: Detailed Tables 2013)

Epidemiology: Women and substance use disorders

- Gender-specific effects of substances on women:
  - Shorter times from first use to developing SUD—telescoping effect (Khan 2013; Randall 1999)
  - Women experience greater impairments in employment, social, psychiatric and medical domains compared with men (Hernandez-Avila 2004; McHugh 2013)
  - Women are more susceptible to risky sex and injection practices compared with men (Brooks 2010; Frajzyngier 2007)
- Less than 20% of women who need treatment receive it in a given year (Terplan 2012)

Epidemiology: Substance Use Disorders & Pregnancy

- Annual prevalence of illicit drug use in pregnant women (6%) is less than that of non-pregnant women
  - Prevalence of illicit drug use is highest amongst young pregnant women (18.3% among 15-17 year olds, and 3.4% among those 26-44) (NSDUH 2012)
- Approximately 1.6% of pregnant women meet criteria for substance use disorder (Vesga-Lopez 2008)

Epidemiology: Opioid Use Disorders & Pregnancy

- Of all substances, for men and women, opioids account for the greatest number of overdose deaths (Calcaterra 2013)

- In a 2008 retrospective study looking at universal Utox screening at delivery, 2.6% of pregnant women tested positive for opiates at large urban teaching hospital in New Orleans (Azadi 2008)

Opioid Use Disorders: Maternal Risks

- Infectious Diseases:
  - HIV
  - Hepatitis B and C
  - Other infections related to use: cellulitis, endocarditis
- Overdose
- Pain management: before, during, and after delivery
- Psychosocial challenges often co-occurring with opioid use disorders: prostitution, theft, violence to support habit(s), domestic violence, incarceration and other legal problems, poor engagement in prenatal care
- Psychiatric comorbidities: depression and anxiety along with opioid use disorders lead to worse treatment outcomes (Benningfield 2012)

Opioid Use Disorders & Pregnancy: Fetal/Risks Risks

- Low birth weight (Hulse 1997)
- Birth defects (congenital heart defects associated with first trimester codeine exposure) (Zierler 1985; Bracken 1986)
- Fetal growth restriction
- Abruptio placentae, fetal death, preterm labor, and intrauterine passage of meconium
  - Postulated to be related to withdrawal/intoxication cycles of mother
  - (Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy 2008)

Opioid Use Disorders & Pregnancy: **IMPORTANT NOTE**

- Heroin readily crosses the placenta, and pregnant women using heroin (untreated) have a 6-fold increase in risk of obstetrical complications and a 74-fold increase in risk of sudden infant death syndrome (Dattel 1990; Fajemirokun 2006; Ludlow 2004)
  - Much of this risk is attributed to repeated cycles of withdrawal experienced by the pregnant women and fetus
- While both buprenorphine and methadone carry risks (as illustrated in subsequent slides), these risks are felt to be minor relative to ***ongoing untreated*** heroin or other non-medical opioid use
  - Both methadone and buprenorphine allow for more steady blood levels of opioids (Jarvis 1994, Rayburn 2004, respectively) that prevents exposure to repeated fetal/maternal withdrawal events.
  - It is important to know these relative risks/benefits when discussing treatment options with a pregnant woman

Opioid Use Disorders & Pregnancy: Neonatal abstinence syndrome

- **Neonatal abstinence syndrome (NAS)** (Patrick 2012; Kaltenbach 1998):
  - Dysregulation in central, autonomic and GI system functioning (Finnegan 1991)
    - CNS features include high-pitched cry, reduced quality and length of sleep, increased muscle tone, tremors, convulsions
    - Autonomic features include yawning, sweating, sneezing, increased respiratory rate
    - GI features include excessive sucking, poor feeding, regurgitation or vomiting, loose stools
  - Usually starts within 24 hours after birth (heroin) to 72 hours after birth (methadone and buprenorphine), but may be delayed up to 5 to 7 days in some infants

Opioid Use Disorders & Pregnancy: Neonatal abstinence syndrome

- 3-fold increase in infants born with NAS in US in past 10 years (Patrick 2012)
- Treatment: opioid supplementation (usually morphine; buprenorphine and methadone have also been used) then taper for 8-12 days (Brown 2011; Patrick 2012; Osborn 2010)
  - e.g., Morphine 0.24 to 1.3 total mg/kg/day dosed q 3-4 hrs (O'Grady 2009)
- Pharmacologic interventions required by 50-70% of infants (depends on genetic factors, other drug exposures, gestational age, breastfeeding) (Patrick 2012)
- Severity of NAS assessed by instrument (e.g., Finnegan Neonatal Abstinence Severity Score (FNASS), Lipsitz Tool, Neonatal Withdrawal Inventory)
  - Data does not one scale over another, but FNASS is widely used (modified version of which was used by Jones, et al. in 2010 MOTHER study)
    - FNASS assessed q 1-4 hours: cry, sleep, muscle tone, yawning, sweating, sneezing, tachypnea, vomit, poor feeding, diarrhea (Lim 2009)

Opioid Use Disorders & Pregnancy: Costs

- 2009 Costs associated with treatment of neonates exposed to opioids estimated between $70.6 mill to $112.6 mill in U.S. (Jones 2011; Kandall 1993)

Opioid Use Disorders & Pregnancy: Screening

- Set the stage—address confidentiality concerns/policies
- Examine for signs/symptoms of use/intoxication/withdrawal
  - Sedation, erratic behavior, track marks, “skin popping” intradermal injection lesions, abscesses, cellulitis, urine toxicology positive (only with patient consent and compliance with state laws)

Opioid Use Disorders & Pregnancy: Screening Tools—4Ps

- 4 P's/4 P's Plus (Ewing 1990; Morse 1997)
  - **P**arents—did either of your parents ever have a problem with alcohol or drugs?
  - **P**artner—Does your partner have a problem with alcohol or drugs?
  - **P**ast—Have you ever drunk beer, wine, or liquor?
  - **P**regnancy—In the month before you knew you were pregnant, how many cigarettes did you smoke? In the month before you knew you were pregnant, how many beers/how much wine/how much liquor did you drink? In the month before you knew you were pregnant, how many times did you use opioids non-medically?
  - Downside: copyrighted and cannot be used without permission

Opioid Use Disorders & Pregnancy: Screening Tools—CRAFFT

- CRAFFT (Chang 2011)—validated in pregnant women, in addition to adolescents
  - Have you ever ridden in a **car** with someone (including yourself) who was "high" or had been using alcohol or 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, **alone**?
  - Do you ever **forget** things you did while using alcohol or drugs?
  - Do your family or **friends** ever 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?
  - Advantage: Open-source

Opioid Use Disorders & Pregnancy: Screening Tools—Other

- TWEAK:
  - **T**olerance, **W**orried, **E**ye-Opener, **A**mnesia, **K**/Cut Down
  - Validated screen for peri-conceptual risky *drinking* (Russell 1994)
- T-ACE:
  - **T**olerance, **A**nnoyance, **C**ut Down, **E**ye-Opener
  - Validated screen for peri-conceptual risky *drinking* (Russell 1994; Sokol 1989)
  - Vs. **CRAFFT** (Chang 2011)—CRAFFT better at detecting past 6 month usage of drugs or alcohol, T-ACE better at picking up lifetime alcohol use

Opioid Use Disorders & Pregnancy: Mandatory reporting considerations

- Mandates regarding reporting of mothers with substance use problems to child services agencies vary from state to state
  - 17 states consider maternal substance use “child abuse”
    - 3 states consider it grounds for civil commitments (MN, SD, WI)
  - 15 states require health care providers to report suspected prenatal substance abuse
    - 4 states require them to test if they suspect it
  - 18 states have targeted programs for pregnant women
  - 10 states provide pregnant women with priority access to state substance abuse programs
  - For more information refer to:
    - http://www.guttmacher.org/statecenter/spibs/spib_SADP.pdf

Opioid Use Disorders & Pregnancy: Mandatory reporting considerations

- Example:
  - Massachusetts:
    - Requires that all healthcare providers file a report to the state's department of children and families (DCF) on every mother who is in medication assisted treatment (MAT) for opioid dependence (buprenorphine or methadone)
      - DCF will not investigate if patient is in good standing with methadone or buprenorphine treatment clinic/provider
      - See: http://www.mass.gov/eohhs/docs/dph/quality/hcq-circular-letters/2013/dhcq-1305586-sen-guidelines.pdf

Opioid Use Disorders & Pregnancy: Mandatory reporting considerations

- Example:
  - California:
    - Positive urine toxicology screen in infant born to mother either in or not in MAT does not mandate reporting. It is at the discretion of the provider to assess the need for reporting to county welfare department, police, or probation department
      - See: http://mandatedreporterca.com/images/Pub132.pdf

Opioid Use Disorders & Pregnancy: Medication Assisted Treatment (MAT)

- Maternal withdrawal from opioids has been associated with deleterious effects on the fetus, such as miscarriage, with the 1st and 3rd trimesters being particularly vulnerable periods (Luty 2003; McCarthy 2012)
  - In the US and many European countries, the recommended treatment of opioid dependence in pregnant women is opioid maintenance therapy (World Health Organization 2009)
- As with outcome measures in non-pregnant individuals, use of MAT (buprenorphine or methadone) as part of a comprehensive care approach to pregnant woman improves maternal and neonatal outcomes (Jones 2011; Winklbauer 2008; Kaltenbach 1998)

Opioid Use Disorders & Pregnancy: Medication Assisted Treatment (MAT)

- There are three general categories of MAT:
  - Mu opioid antagonism with **naltrexone**
  - Mu opioid agonism/partial agonism with either:
    - **Methadone**
    - **Buprenorphine**

Opioid Use Disorders & Pregnancy: Naltrexone

- Pure opioid antagonist at mu, kappa, and delta opioid receptors (highest affinity for mu)
- Available in oral and long-acting injectable forms
- Food and Drug Administration (FDA) safety category in pregnancy: C
  - Meaning: either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.

Opioid Use Disorders & Pregnancy: Naltrexone

- Not currently approved or recommended in pregnancy
- Benefits:
  - no risk of NAS
  - NOT a controlled substance (does not require special licensure)
- Risks:
  - Long-term effects on fetal development due to blockade of opioid (mu, kappa, delta) receptors is not well known. Animal studies have shown developmental and behavioral changes in adult rats exposed to naltrexone in utero, but humans studies on developmental and behavioral sequelae are lacking (Farid 2012; White 2013).
  - Requires detoxification from opioids
  - High rates of relapse/dropout from treatment (Waal 2013)
  - Possible complications for pain management during and post-delivery

Opioid Use Disorders & Pregnancy: Methadone

- Synthetic Mu opioid receptor agonist and N-methyl-D-aspartate (NMDA) receptor antagonist
- FDA safety category in pregnancy: C
  - Considered standard of care for MAT in pregnant women in US, although NOT FDA approved for this indication
- Crosses placenta

Opioid Use Disorders & Pregnancy: Methadone

- Methadone is the most commonly used MAT for opioid dependency in pregnancy in U.S.
- Requires engagement in federally sanctioned methadone treatment programs/clinics (42 Code of Federal Regulations (CFR) Section 8.12)
- Mandated reporting

- **Benefits:**
  - Pregnant women in MTPs have improved fetal outcomes compared to pregnant women using illicit drugs (ACOG 2012)
  - Structured clinic setting with additional substance use disorder treatment programming

Risks of Methadone Use in Pregnancy

- **Risks:**
  - Fetal growth, birth weight, length, and/or head circumference may be decreased but these effects do not appear to persist (ACOG 2012)
  - Decreased psychometric and behavioral tests has been found to persist into childhood (ACOG 2012)
  - NAS up to 2-4 weeks after delivery
  - Increased clearance and decreased half-life in pregnant women (2nd and 3rd trimesters) requiring increased dosing amounts and frequencies, and decrease after delivery (ACOG 2012)
  - Many drug-drug interactions
  - QTc prolongation, constipation, diaphoresis
  - May complicate pain management acutely, owing to blockade of mu receptors

Opioid Use Disorders & Pregnancy: Buprenorphine

- High-affinity Mu opioid receptor partial agonist and kappa opioid receptor antagonist
- FDA safety category in pregnancy: C
- Crosses placenta
- Available in diversion-deterrent formulation combined with naloxone
- Recommendation in pregnancy is to use buprenorphine alone, due to potential risks posed by naloxone

Opioid Use Disorders & Pregnancy: Buprenorphine

- **Benefits:**
  - Office based: does not require clinic, although some buprenorphine clinics available for daily dosing
  - Ceiling effect for respiratory suppression (although this is eliminated when using benzodiazepines concurrently)
  - Maintain in treatment
- **Risks:**
  - NAS
  - Constipation, diaphoresis
  - Possible complications for acute pain management due to high affinity blockade of mu opioid receptors
  - Lower head circumference and birth weights (Hytinantii 2008)
  - Need for safeguarding medication

Opioid Use Disorders & Pregnancy: Buprenorphine vs. Methadone

- Multi-site randomized controlled trial (Jones et al, 2010)
- **Buprenorphine:**
  - Fewer dose adjustments
  - Fewer drug-drug interactions
  - Ceiling effect
  - Office-based
  - Less NAS, shorter hospital stays (Jones, et al, NEJM, 2010)
  - More drop-out relative to methadone (33% vs. 18%, respectively) (Jones, et al, NEJM, 2010)
- **Methadone:**
  - More available data on long-term developmental and behavioral outcomes
  - Structure provided by clinic setting
  - Potentially easier acute pain management relative to buprenorphine
  - More familiarity amongst hospital staff and other providers

Opioid Use Disorders & Pregnancy: Buprenorphine vs. Methadone

- "The current trend is moving toward considering a patient as a potential candidate for buprenorphine if she prefers buprenorphine to methadone, gives informed consent after a thorough discussion of relative risks and benefits, and is capable of adherence and safe self-administration of the medication. If the pregnant woman is receiving methadone therapy, she should not consider transitioning to buprenorphine because of the significant risk of precipitated withdrawal. The potential risk of unrecognized adverse long-term outcomes, which is inherent with widespread use of relatively new medications during pregnancy, should always be taken into consideration." (ACOG 2012)

Opioid Use Disorders & Pregnancy: MAT and Lactation/Breastfeeding

- Breastfeeding is beneficial to infant and mother
  - Mother-infant bonding (Tharner 2012)
  - Infant benefits: Decreased incidence of otitis media, gastroenteritis, severe lower respiratory tract infections, childhood leukemia, type 1 & 2 diabetes, obesity, asthma, sudden infant death syndrome, and necrotizing enterocolitis (Ip 2007)
  - Mother benefits: Decreased incidence of type 2 diabetes, breast/ovarian cancer, and post partum depression (Ip 2007)

Opioid Use Disorders & Pregnancy: MAT and Lactation/Breastfeeding

- Naltrexone
  - Enters breast milk (manufacturer does not recommend breastfeeding while on this medication)
  - Little data on its safety for use in breastfeeding (animal data demonstrates some potential tumorigenicity—product information, Vivitrol 2010)
- Some evidence of reduced NAS in women who have been on opioid agonist/partial agonist maintenance during pregnancy (Welle-Strand 2013)

Opioid Use Disorders & Pregnancy: MAT and Lactation/Breastfeeding

- Buprenorphine
  - Excreted in breast milk
    - Manufacturer does not recommend breastfeeding while on this medication
    - However, most guidelines do not contraindicate usage while breastfeeding (ACOG 2012; CSAT 2004; Montgomery 2012)
    - Little is bioavailable to infant, owing in part to the need for sublingual absorption [Samples from single mother-infant pair demonstrated daily infant ingestion of 3.28mcg from a lactating mother receiving 4mg daily (Marquet 1997)]

Opioid Use Disorders & Pregnancy: MAT and Lactation/Breastfeeding

- Methadone
  - Excreted in breast milk
    - Dose to a nursing infant is 2-3% of maternal dose (10-80mg maternal methadone daily dosing)
  - Manufacturer does not recommend breastfeeding while on this medication
  - However, most guidelines do not contraindicate usage while breastfeeding (ACOG 2012)
  - If illicit drugs are being used while mother is taking methadone, it is recommended that breast milk is pumped and discarded until sobriety is achieved (ACOG 2012; Dow 2012)

Opioid Use Disorders & Pregnancy: Behavioral Approaches

- Overall, little research has been done specifically on behavioral treatments of opioid dependence in pregnant women
- Motivational enhancement therapy (MET)
  - One session: reductions in *alcohol* drinks per drinking day (Ingersoll 2013)
- Screening coupled with brief intervention (MET)
  - Four session manualized MET reductions in prenatal *alcohol* exposure (Velasquez 2010)
- Contingency management
  - Reduction in cocaine use in pregnant women in methadone maintenance using escalating voucher incentive schedule (Jones 2001)
  - Low magnitude incentives enhanced program attendance by pregnant women in methadone maintenance (Jones 2000)

Summary I

- Substance use disorders are less prevalent in women than in men, but gap is closing. Some features of SUDs present uniquely in women.
- Substance use disorders are less common in pregnant women than in non-pregnant women.
- Opioid use disorders present a host of risks to pregnant women including infections, pain management, psychosocial problems, overdose and co-occurring psychiatric disorders.
- Opioid use disorders also present an array of risks to the fetus/newborn including premature labor, placental problems, low birth weight, neonatal abstinence syndrome
- There are several validated screening tools for detecting opioid and substance use disorders in pregnant women.
- Mandatory reporting requirements vary by state.

Summary II

- Naltrexone is currently not advised for use during pregnancy due to lack of long-term developmental data.
- Neither methadone nor buprenorphine is FDA-approved for use during pregnancy, but a growing literature suggests their benefits.
- Methadone and buprenorphine have several advantages/disadvantages relative to one another, and ultimately a conversation about these with a pregnant women who is considering these medications is indicated.
- Naltrexone, buprenorphine, and methadone are all found in breast milk, and decisions regarding their use should be made with the patient in the context of the relative risks/benefits of each of these approaches.
- Several behavioral approaches to the treatment of substance use disorders have been validated in pregnant women, but most of this data are for women with alcohol use disorders.

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