Illicit Drug Use in Pregnancy

Deirdre Lyell, MD
Professor, Obstetrics and Gynecology
Program Director, MFM Fellowship
Director, Program in Placental Disorders
Stanford University Medical Center
UCSF AIM Conference
June 9, 2016

Disclosures

- I have the following relationship:
  Bloom Technologies - Advisor

I have no disclosures related to the content of this presentation

Objectives

- Overview of:
  - current patterns of drug use and specific issues
  - pregnancy morbidities of specific drugs
    - Marijuana, opiates/methadone
  - neonatal abstinence syndrome (NAS)
  - screening
  - breastfeeding
  - anesthetic issues, pearls

Why this topic?

- Obstetric providers:
  - Screen, diagnose, educate, counsel, initiate treatment

- Time of increased motivation
  - Pregnancy-related abstinence among users: 57%
  - Resumption of use first year after pregnancy is lower than that of non-new mothers
What is the most frequently used illicit drug in the U.S.?
A. Prescription pain relievers
B. Hallucinogens
C. Cocaine
D. Marijuana

Patterns of use in U.S. (2012-2013)
- Ages 15-44: 5.4% of pregnant women used illicit drugs in the last month (versus 11.4% non-pregnant)
  - 15-17 years: 14.6%
  - 18-25 years: 8.6%
  - 26-44 years: 3.2%
- Poly-substance use common
- Not significantly different from 2010-2011

Drugs of Choice in U.S.
- Survey of 67,500 people 12+ years old:
  1\textsuperscript{st} Marijuana
  2\textsuperscript{nd} Psychotherapeutics: non-medical use of pain killers then tranquilizers, stimulants and sedatives
  3\textsuperscript{rd} Cocaine
  4\textsuperscript{th} Hallucinogens

Opiate use is increasing

- 2000: 1.19/1000 births (95% CI 1.01-1.35)
- 2009: 5.63/1000 births (95% CI 4.40-6.71)

Pregnancy Morbidities of Specific Drugs

Limitations of data

- Multiple confounding variables
  - Polypharmacy frequent
    - Other drugs, alcohol, tobacco
  - Poor social circumstances, poverty, late to care or inadequate care, poor nutrition, co-morbidities
  - Incomplete testing/reporting, scarce data
- No prospective studies

Does marijuana cross the placenta?

A. Yes
B. No
Marijuana

- Tetrahydrocannabinol (THC)
  - Small, highly lipophilic molecule, distributes rapidly to brain and fat
  - Half-life varies:
    - 20-36 hours in occasional users
    - 4-5 days in heavy users
    - Can take 30 days for complete excretion
- Crosses the placenta
  - Fetal levels in mouse are initially 10% of ingested levels
  - Higher concentrations seen with repetitive use
- Current products have higher THC content than past

Marijuana

- Most frequent illicit drug in pregnancy
- Prevalence (2-5% overall) increases to 30% among urban, socioeconomically disadvantaged young women
- Approximately 50% continue use during pregnancy
  - Belief that it is relatively safe
  - Less expensive than tobacco

Marijuana

- No high-quality data to suggest teratogenic effect
  - Embryotoxic in rabbits
- Several small studies suggest increased low birth weight, preterm birth, SGA and NICU admission
  - Many confounding variables
    - Saurel-Cubizolles et al, BJOG 2014;
- Delayed motor development at 1 year

Marijuana

- Prospective cohort study, n=5588 nulliparous, low-risk women (SCOPE study), 90% Caucasian
- Self-reported marijuana and tobacco use
- Adjusted for maternal age, tobacco, alcohol, SES
- Continued marijuana use at 20 weeks associated with:
  - 5.4 fold increased spontaneous preterm birth (sPTB; 95% CI 2.44-12.11)
    - 11 women: 4 (36%) delivered <28 weeks; 7 <32 weeks (64%)
  - Dose-dependent effect
  - Effect not seen for women who quit <20 weeks
  - No differences in SGA, preeclampsia
- Authors estimated cessation of marijuana would result in 6.2% reduction in sPTB

Leemaqz SY et al, Reproductive Toxicology 62(2016)77-86
Opiates
- Not teratogenic
- Risks: social and withdrawal
- Obstetric issues are difficult to separate from withdrawal, polypharmacy, social issues and other confounding variables
- Multiple problems in pregnancy:
  - Spontaneous abortion, IUGR, stillbirth, intra-amniotic infection, abruption, preeclampsia, preterm labor and delivery, PPROM, placental insufficiency, postpartum hemorrhage, septic pelvic thrombophlebitis

How many hours since last use do heroin withdrawal symptoms peak
- A. 12 hours
- B. 16 hours
- C. 24 hours
- D. 48 hours
- E. 60 hours

Heroin withdrawal

Risks of withdrawal
- Maternal: relapse, increased drug seeking behaviors
- Fetal withdrawal (intrauterine abstinence syndrome, IAS):
  - Remenéria et al., 1973 (AJOG): term stillbirth following narcotic withdrawal
  - “A high percentage of mothers who are detoxified revert back to heroin….wiser to encourage methadone programs to ‘maintain’ rather than ‘withdraw’ the addict during pregnancy?”
  - Zuspan et al., 1975: elevated amniotic fluid epinephrine levels during methadone detox despite normal maternal catecholamine levels, improved with increased methadone dose
  - Wang W et al., 1997, Case report of withdrawal in 29 week EGA with IUGR and AEDF. Dopplers returned to normal after administration of methadone
  - Suggests withdrawal can reversibly affect fetal placental circulation
### Opiates: substitution therapy recommended

- Preferable to withdrawal: safe, lower rate of resumption of heroin
- Methadone or buprenorphine
  - Oral administration, known dose, available, improved maternal/fetal/neonatal outcomes
- Methadone shown to:
  - Increase fetal weight
  - Improve compliance with prenatal care
  - Reduce exposure to illicit substances
  - Potentially improve custody retention rates due to less frequent relapse
    - Cochrane Reviews, 2008; Messinger Pediatrics 2004
- Emphasizes importance of stabilizing the home for child development
- At 3 years old, no difference in outcomes after corrected for confounding social factors

### Neonatal Abstinence Syndrome (NAS)

**What is NAS?**

- Array of newborn signs and symptoms after birth in the setting of fetal drug exposure (typically opioids: heroin, methadone, hydrocodone [vicodin], oxycodone [oxycontin])
- Often seen at 24-48 hours, may be delayed as long as 10 days
- Akin to CNS overstimulation

https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/substance-use-while-pregnant-breastfeeding

NIH: National Institute on Drug Abuse

### What is NAS?**

- Excessive or continuous high pitched crying
- Sleeps less than 1 hour after feeds
- Hyperactive Moro reflex
- Tremors, myoclonic jerks, generalized seizures
- Withdrawal signs: sweating, frequent yawning, moaning, nasal stuffiness, sneezing, nasal flaring, tachypnea, excessive sucking, poor feeding, regurgitation, vomiting, loose or watery stools, fever

**Treatment:** first supportive with IV fluids, extra calories, comfort; if more severe, pharmacotherapy (oral morphine or methadone) with wean

https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/substance-use-while-pregnant-breastfeeding

NIH: National Institute on Drug Abuse
Methadone dose not predictive of NAS severity

- Retrospective review, 100 mother/infant pairs on methadone
- <80 mg versus >80 mg
- No difference in highest NAS score, need for or length of treatment
- More illicit use if <80 mg
  - Berghella V et al, AJOG 2003
- Retrospective review of 81 mother/infant pairs on methadone
- <100 mg versus >100 mg
- No differences in need for treatment of NAS or length of stay
- More illicit substance abuse at delivery if <100 mg
  - McCarthy JJ et al, AJOG 2005
- Higher methadone doses may decrease illicit drug use and high risk behaviors

Scope and cost of NAS

- Increasing with increasing opiate use
- Among 650,000 neonates born in U.S. 2004-2013
  - NAS increased from 7 cases/1000 NICU admissions to 27 cases/1000
    - 3.86-fold increase
  - Total NICU days for NAS increased from 0.6% to 4.0%
    - Tolvia VN et al., NEJM 2015
- 42-94% infants of opiate abusers experience NAS
- In 2011: $750,000,000 in NICU charges (US)

Stanford Study: Prevention of NAS

- Ondansetron reduces opiate withdrawal in adults and animals
- Double-blind, placebo controlled, randomized study of 90 neonates born to 90 opioid-dependent mothers
- Inclusion: pregnant women 18-45 years, singletons, term (37 to <42 weeks), opioids for at least 3 weeks prior to delivery, vaginal delivery or cesarean
- Ondansetron
  - If possible: I.V. at least 30 minutes prior to delivery
  - Newborn: oral or I.V. ondansetron qD x 5 days, beginning 4-8 hours of life
- Primary outcome: incidence NAS

Protocol

- Study sites: Stanford, UCSF, SCVMC, University of Utah, Johns Hopkins University
- NIH/NICHD R01-funded study, PI David Drover, MD
- Research coordinator:
  - Carol Cohane, RN, 650-736-8231
  - cohane@stanford.edu
MATERNAL SCREENING

Screening
- ACOG recommends universal screening
- Incidence similar among all socioeconomic strata and races
- When universal screening not conducted during pregnancy, use was identified in only 1/3 of women who later had child removed from home for parental substance abuse
  - Wallman CM et al. Adv Neonatal Care 2011
- Screen at first prenatal visit
  - Consider repeat screening
  - Each trimester?

Screening questions: CRAFFT
- C-ridden in CAR driven by someone/high?
- R-ever use to RELAX, feel better or fit in?
- A-ever use ALONE?
- F-ever FORGET things done while using?
- F-FAMILY or friends tell you to cut down?
- T-ever been in TROUBLE while using?
- Two or more: needs further assessment
- Better than T-ACE for prenatal screening

Risk factors/flags
- Young, unmarried, lower education
- Late prenatal care
- Multiple missed appointments
- Impaired work or school performance
- Change in behavior
- STIs
- Unstable home
- Unexplained adverse events in obstetric history (SAB, abruption, IUGR, stillbirth, precipitous delivery)
Risk factors/flags
- Children not living at home
- History of cellulitis, skin abscess, endocarditis, hepatitis
- Poor dentition
- Poor weight gain
- Mental health disorder diagnosis
- Partner who is a substance abuser

What to do if positive screen?
- Discuss with patient
- Discuss risks
- Refer based on available resources
- Follow up
- Rescreen
- HIV status?

Event-based Laboratory Testing?
- No consensus. Consider screen if:
  - abruption, PTL, IUGR, unexplained demise, poor PNC/non-compliance, frequent requests prescription drugs
- Informed consent

Reporting
- State laws vary
- 2014+: Tennessee, Alabama, South Carolina criminalized drug use in pregnancy
  - https://projects.propublica.org/graphics/maternity-drug-policies-by-state
- 18 states: consider prenatal drug exposure child abuse or neglect, potential grounds to terminate parental rights
- 3 states authorize involuntary commitment to inpatient treatment programs
- Some states mandate testing and reporting
- Some prioritize making drug treatment more available
- Federal funding requires priority access to treatment programs for pregnant women
  - www.guttmacher.org, accessed May 2016
California

- Substance abuse in pregnancy not considered a crime
- 1977 indictment, appeals court overruled
- Not grounds for commitment
- Testing not mandated if use suspected
- No specific law mandating reporting
- No specific law considering use child abuse

ACOG

“Seeking obstetric-gynecologic care should not expose a woman to criminal or civil penalties, such as incarceration, involuntary commitment, loss of custody of her children, or loss of housing. These approaches treat addiction as a moral failing”

Benefits of breastfeeding

- Nutrition
- Promotes attachment
- Oxytocin release increases maternal euphoria and pain tolerance
- Skin to skin contact may help some NAS symptoms

Should women using marijuana breastfeed?

A. Yes
B. No
C. Depends

51% 32% 17%

Marijuana

- Breast feeding
- Limited data suggest passage to breast milk
- ACOG and Academy of Breastfeeding Medicine do not recommend

Should opioid-dependent women breastfeed?

A. Yes
B. No
C. Depends

0% 0% 0%

Methadone and breastfeeding

- Until 2001 AAP recommended against breastfeeding with methadone doses > 20 mg/day
- AAP: usually compatible with breastfeeding
  - If stable, in program, abstinent from other drugs, negative urine tox screen at delivery
- WHO Working Group on Lactation: compatible with breastfeeding
- US study of 20 lactating women (treatment dose 40-200 mg, mean 102 mg/day)
  - Infant dose is 2.7% (0.7-10.1%) of the maternal dose
  - Even at higher maternal doses, infant doses were low

Methadone and breastfeeding

- Shorter hospital stay
  - Retrospective study of 190 infants of opiate-dependent women
    - Finnegan scores (assessment of NAS severity) lower in the breastfed group vs. formula-fed group
    - Fewer infants in the breastfed group required treatment
  - Retrospective study of 121 infants of methadone-maintained mothers
    - Infants treated for NAS that were breastfed went home an average of 8 days earlier than those who were formula-fed


Opioids and breastfeeding

- Hydrocodone, codeine: “Infant risk cannot be ruled out”
  - Poor clearance in neonates
  - Ultra-rapid metabolizers

Anticipatory Guidance

- Neonatal withdrawal symptoms may hinder or delay the establishment of successful breastfeeding
- Mothers may become frustrated by inconsolability, frantic sucking, and feeding difficulty
- Lactation consultants

OTHER:
ANTENATAL TESTING, ANESTHESIA, PEARLS
**Antenatal testing?**

- Retrospective study
- n=707 self-reported substance use during pregnancy among 89,080 pregnancies
- Adjusted odds ratio for stillbirth: 2.54
  - Kennare R et al., Aust New Z Obstet Gynecol, 2005

- Increased IUGR associated with illicit drug use

- Limited data but common sense: non-stress tests, growth ultrasounds

**Anesthetic considerations in opioid dependence**

- Similar benefit from regional anesthesia
- Vaginal delivery: increased pain 24 hours pp
  - Routine postpartum orders with PRN opioid analgesics
- Cesarean: 70% increase in opioid requirement pp
  - 1st 24 hours: consider morphine or hydromorphone PCA
  - >24 hours: short-acting opioid (hydromorphone), 50-70% increased dose (4-6 mg PO q4-6 hours), same treatment duration
- BEWARE: nalbuphine (Nubain) and butorphanol (Stadol) are partial opioid agonist-antagonists and can cause acute withdrawal

**One more: cocaine**

- Crosses the placenta and blood-brain barrier
- Causes vasoconstriction
  - PTB (OR 3.38), GA at delivery (-1.47 weeks), decreased BW (-492 grams), LBW (OR 3.66)
  - SAB, abruption, decreased length and HC
- Hypertension: avoid labetolol (creates unopposed alpha-adrenergic stimulation; coronary vasospasm)
  - Hydralazine is preferred
  - Individualize anesthetic decisions
- Hypertension: avoid labetolol in cocaine-induced hypertension

**Conclusions**

- Marijuana linked to increased spontaneous preterm birth; much more data coming out now due to increased prevalence
- Opiates: substitution therapy recommended, detox in pregnancy not recommended
- Breast feeding ok in methadone maintenance programs, not recommended with marijuana
- Anesthetic adjustments are needed in chronic opioid users, especially following cesarean delivery
- Avoid labetolol in cocaine-induced hypertension
Illicit Drug Use in Pregnancy

Deirdre Lyell, MD
Professor, Obstetrics and Gynecology
Program Director, MFM Fellowship
Director, Program in Placental Disorders
Stanford University Medical Center
UCSF AIM Conference
June 9, 2016