Substance Use and Substance Use Disorders in Pregnancy: Clinical Considerations

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Learning Objectives

- Understand the scope of the problem with substance use and abuse disorders during pregnancy
- Identify the most commonly encountered substances used by pregnant women and their effects on the fetus/neonate
- Assess the impact of recreational use of marijuana on fetal growth and development
- Describe the identification and management of withdrawal in pregnant women and newborns
- Determine appropriate breastfeeding recommendations for women with substance use disorders (SUD)
Substance Use and Substance Use Disorders in Pregnancy

• Substance Use Disorder (SUD):
  • Recurrent use of substances that cause clinically significant impairment + failure to meet major responsibilities

• 2014: 27M reported using drugs in last 30 days (10.2%)
  • Lead by marijuana use and prescription pain meds

• Pregnant women: 123K reported using drugs in last 30 days (5.3%)
  • Use did not differ by race in latest survey
  • Highest rates in younger women and in the 1st trimester

• Validated screening tools
  • 4P’s and CRAFFT


Type and Recency of Substance Use in Pregnant Women: 2013/2014 NSDUH Data

- Within past 30 days
- 30+ days - 12 months

- Cigarettes: 49.8%
- Alcohol
- Marijuana
- Pain Meds
- Tranquilizers
Type and Recency of Substance Use in Pregnant Women: 2013/2014 NSDUH Data

How Does Idaho Compare Nationally?
Clinical Care of the Substance Using Pregnant Mother - Maternal and Fetal Considerations

Limitations of Available Evidence

1. Concurrent use of multiple substances is common
2. Accurate determination of fetal exposure is difficult
3. Many substance-using women are economically disadvantaged
   • Poor maternal nutrition, hygiene, and prenatal visit attendance - ALL have adverse perinatal effects!
4. Small population sizes & unblinded evaluations of drug-exposed newborns may bias associations
   • Most evidence is “suspected” and not truly “causal”
   • Lack of uniformity in defects and failure to use pregnant controls
5. Except alcohol, a birth defect syndrome has not been described for any illicit substances or prescription drugs of abuse
   • Risk of stillbirth and/or miscarriage increases from use of any drug
6. Altered fetal behaviors: insidious, variable, hard to recognize

Holbrook and Rayburn, 2014
Tobacco Use and Dependency

- Nicotine concentrations are higher in fetal compartment
  - ~30 compounds associated with adverse outcomes cross placenta

- Etiology of the adverse effects are not well understood
  - Hypoxia, undernourishment, vasoconstriction
  - PTB, placenta previa, placental abruptio, possible reduced risk for pre-eclampsia*

- Identified as a preventable risk factor for LBW and IUGR for >50 years
  - Decreased birthweight has some indication of dose-effect relationship
  - By 24 mos, somatic growth differences disappear

- No “convincing” studies of neonatal nicotine withdrawal
  - Abnormal newborn behavior more consistent with drug toxicity than with drug withdrawal
    - Impaired orientation and autonomic regulation plus abnormalities of muscle tone
    - Higher neonatal irritability, increased need for handling to quiet newborn

Clinical Care of Tobacco Dependency in Pregnancy

- Quitting <15wks = greatest benefit
  - <28wks = eliminates much of the reduction in birth weight

- 50-60% women who quit smoking in pregnancy return to smoking within 1 year postpartum

- Smoking Cessation Interventions
  - Counseling - including twice weekly phone calls during pregnancy and monthly calls after delivery +/- contingency management (i.e. financial incentives)
  - 5 A’s Motivational Interviewing - Ask, Advise, Assess, Assist, Arrange
  - Nicotine replacement products - Conflicting evidence of increased rates of abstinence in pregnant smokers yet often used in-patient
  - Bupropion - Limited efficacy data, no risk of fetal anomalies/adverse pregnancy effects
  - Varenicline - No data on safety or efficacy during pregnancy

- Lack of information regarding vapes or e-cig use in pregnancy

ACOG Committee opinion no. 471, 2010
Alcohol Use and Dependency

- >50% women smoking in the 1st trimester also drink
- >50% women using illicit drugs during pregnancy also report smoking, drinking or both

- Alcohol (EtOH) crosses placenta easily, with significant concentrations in amniotic fluid and fetal blood
  - Alters prostaglandin/protein synthesis; hormones; neurotransmitter levels in the brain; brain morphology; neuronal development; hypoxia due to decreased placental blood flow and altered vascular tone

- Fetal Alcohol Spectrum Disorders
  - One of most common, preventable causes of developmental and intellectual disabilities in US
  - Combination of physical, neurological, behavior and learning problems
  - Includes: Partial FAS (PFAS), Alcohol-related Birth Defects (ARBD), Alcohol-related Neurodevelopmental Disorder (ARND)*, and Neurodevelopmental Disorder Associated with Prenatal Alcohol Exposure (ND-PAE)*


Clinical Care of Alcohol Dependency in Pregnancy

- Infants with FASDs characterized by poor suck and irritability
  - Benefit from nutritional support and decreased environmental stimulation
  - Poor self-soothing is most common presenting symptom

- No known “safe” amount or timing of alcohol in pregnancy
  - Assess use on monthly basis
    - Increase awareness of risks associated with alcohol use in pregnancy
    - Introduce harm-reduction strategies for women that continue to drink
    - Identification of risky drinking behavior with T-ACE screen
      - Tolerance - Annoyance, Cut-Down, Eye-Opener

- Pharmacotherapy for Alcohol Withdrawal in Pregnancy
  - Thiamine: 100 mg orally once daily for 3 days + folic acid 5 mg orally once daily
  - Diazepam: 20 mg orally every 1-2 hours until symptoms subside
  - Lorazepam: 2-4 mg sublingually or orally every 1-2 hours as needed during labor

Wong S et al, 2011; Carson G et al, 2010
Marijuana Use and Dependency

- One of most widely used psychoactive drugs in the world, following tobacco and alcohol
  - Accepted as relatively harmless recreational agent
- 85 cannabinoids have been identified
  - Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) most abundant
  - THC = only cannabinoid with psychoactive properties

- Endocannabinoids (naturally occurring) regulate movement, memory, appetite, body temperature, pain and immunity
  - 5 cannabinoid receptors identified
    - CB1 (CNS) is involved in critical neurodevelopmental events
      - Present in all layers of the placenta
      - Stimulation may impair fetal growth by inhibiting cytotrophoblastic proliferation
  - Small, lipophilic molecules (i.e. THC) readily cross BBB and placenta
    - THC levels 3-6x lower in cord blood vs maternal blood

Clinical Care of Marijuana Dependency in Pregnancy

- Evidence of fetal effects controversial
  - Lack of human studies or ambiguous outcomes

- Largest study (France) found marijuana use increased risk for PTB and SGA for ≥ once/month users compared to no use
  - Analysis could not distinguish effect of tobacco smoking from cannabis smoking

- 5yr record linkage data demonstrated concurrent cannabis use with other substance use, prompting investigation for SUD in these women
  - 12% concurrently used opioids and 10% concurrently used stimulants
  - 4% identified as having an alcohol-related diagnosis
  - 50% reported smoking >10 cigarettes per day

- Neurobehavioral disturbances in newborns have been noted
  - Exaggerated/prolonged startle reflex; increased hand-mouth behavior; high pitched cries; sleep cycle disturbances; increased incidence of SIDS
  - Little evidence that prenatal exposure affects behavior or cognition in infancy

Jaques SC et al, J Perinatol 2014

Past Month Marijuana, Cigarette or Alcohol Use

After childbirth, use rebounds quickly!

Warner TD et al, Clin Perinatol 2014

Stimulant Use and Dependency: Caffeine

- Quantifying Caffeine - often underestimated!
  - Coffee
    - Starbucks Venti Coffee: 415mg
    - Panera Coffee: 189mg
  - Tea
    - Tazo Awake: 135mg
    - Green Tea: 30-50mg
  - Soda
    - FDA official limit for soft drinks: 71mg
  - Energy Drinks
    - 5 Hour Energy: 208mg
    - Monster/Rockstar: 160mg

- Caffeine metabolized by CYP1A2
  - AHR gene regulates CYP1A2 expression
  - CYP1A2 activity is decreased 65% in pregnancy
    - Half-life of caffeine in pregnancy: 8.3h v 3.4h (adults)

- 2011 GWAS study
  - Polymorphisms in AHR and CYP1A2 genes associated with habitual caffeine intake

Juliano and Griffiths, 2005; Cornelis MC et al, PLoS Genet 2011
Clinical Care of Caffeine Dependency in Pregnancy

- Risks of miscarriage, stillbirth, PTB or SGA
  - ACOG: moderate (<200mg/d) is not a risk for miscarriage or PTB
  - BMC Meta-Analysis: Each 100mg/d increment in maternal intake (>150mg/d) associated with 13% increased risk for low birth weight
  - Eur J Epi Meta-Analysis: Greater intake (>150mg/d) associated with increased spontaneous abortion, stillbirth, low birth weight, SGA but not PTB

- Faster caffeine metabolism in the 2nd trimester associated with reduced risk of subsequent severe pre-E
  - Genetic polymorphisms in CYP1A2 may predispose women w/o other risk factors to caffeine dependency

Stimulant Use and Dependency: Cocaine

- Prenatal cocaine exposure
  - Increases risk of placental abruptio
  - Increases likelihood of PTB and generalized growth retardation
    - Slower growth rates among exposed children through age 10

- Cocaine exposed infants have increased risk of:
  - Tremors/jitters; irritability; excessive suck; hyperalertness; autonomic instability; infections (hepatitis, syphilis, HIV exposure)
  - Higher incidence of NEC
  - Usually transient - acute cocaine/withdrawal effect??
    - ANS/CNS effects additive if fetus exposed to opioids and/or nicotine

- Conflicting evidence concerning language and memory effects during childhood, as well as behavior and attention problems

Clinical Care of Cocaine Dependency in Pregnancy

- No pharmacological intervention shown to be effective
  - Possible role for opioid maintenance treatments for co-occurring cocaine and opioid dependency
  - Interventions based on symptomatic relief only

- Some evidence of efficacy with contingency based (voucher) incentives
  - Combined with CBT, can reinforce abstinence and increase compliance with prenatal care

- Home visits not shown to increase maternal or infant outcomes
  - High loss to followup + other barriers prevent continued utility in treatment programs

- Promising new pharmacotherapy
  - Cocaine Hydrolases
    - Possible Q2-Q4 week dosing regimen
    - Accelerates cocaine metabolism to efficiently detox and inactivate cocaine without affecting normal CNS function (preclinical data)


Stimulant Use and Dependency: Methamphetamines

- Increasing rates of hospitalization d/t amphetamine abuse during pregnancy
  - 50% increase in hospitalizations
    - 82% hospitalizations concentrated in Western US
    - 44% decrease in hospitalizations related to cocaine abuse
  - More commonly associated with maternal vasoconstrictive disorders compared with cocaine abuse
    - Cocaine abuse more commonly associated with dx related to infant mortality compared to amphetamines

- Increased risk of adverse pregnancy and neonatal outcomes
  - Higher incidence neonatal mortality, low birthweight, PTB, Cx delivery
  - Higher rates of 1m Apgar <4 and 5m Apgar <7
  - Higher rates of poor movement quality, decreased arousal, increased stress

Opioid Use and Dependency

- Heroin vs pain narcotics
  - Almost all studies include heroin or agonist maintenance treatments, few examine use of pain narcotics

- Early vs Late use of any opioids in pregnancy (Medicaid data)
  - Long-term use = higher absolute risk NAS with additional risk factors (absolute NAS risk/1000 births)
    - Opioid misuse (220); polysubstance use (31); psychotropic meds (2); smoking (1.5)
    - No risk factors (4.2)
  - Late in pregnancy use = higher absolute risk NAS
    - Late (7.8) vs Early (4.2) use

- Prenatal opioid exposure
  - Decreased birthweight, length and head circumference
  - Increased risk PTB, stillbirth, SIDS, IUGR

Clinical Care of Opioid Dependency in Pregnancy

- Methadone
  - Gold Standard (1970s)
    - Full mu agonist
    - Doses range from 60-300mg/d, potential benefit if divided doses
    - Higher incidence of NAS, especially seizures, compared to buprenorphine and heroin
    - Breastfeeding on methadone seems to assuage NAS symptoms

- Buprenorphine
  - Available treatment option since 2002 with special licensure
    - Less severe (mild) NAS with delayed onset (2-3 days post-delivery)
    - Doses range from 2-32mg/d, often in divided doses
    - Has potential to precipitate withdrawal (partial mu agonist/full kappa antagonist, possible delta/sigmoid activity)
    - Ceiling effect on adverse effects d/t partial mu agonism
Neonatal Abstinence Syndrome (NAS)

- **Prevalence + Incidence data**
  - **Antepartum opioid use**
    - Increased from 1.19/1000 births (2000) to 5.63/1000 births (2009)
  - **NAS incidence**
    - Increased from 1.2 infants/1000 births (2000) to 3.39/1000 births (2009)
    - Using EMR and insurance claim data: NAS absolute risk 5.9/1000 births

- **NAS signs/symptoms**
  - Abnormally high muscle tone/rigidity; inconsolable; irritability; sneezing; stuffiness; excessive sucking; poor sucking ability; high-pitched cry (louder if exposed to cocaine also)
  - Seizures + myoclonic jerks occur in 2-10% NAS infants

  Patrick SW et al, JAMA 2012; Desai RJ et al, BMJ 2015

NAS Treatment Interventions

- **NAS treatments**
  - Supportive care may include
    - Decreasing sensory stimulation
    - Nutrition to promote adequate growth; Breastmilk associated with reduced severity of NAS
    - Prone positioning may reduce severity of NAS, but associated with decreased caloric intake
  - Medications only needed if clinical distress or high withdrawal severity scores
    - Opioids generally recommended, including tincture of opium, morphine, or methadone
    - Opiates may reduce time to regain birth weight and duration of supportive care, but increase duration of hospital stay
    - Sublingual buprenorphine may be associated with shorter hospital stay than oral morphine in term infants
    - Sedatives are not preferred initial treatment
    - Addition of clonidine to opium decreases duration of therapy by 27%
    - Naloxone (Narcan) has insufficient data regarding efficacy and safety
    - No studies evaluating rate at which withdrawal medication should be weaned

Breastfeeding Considerations for Women with SUD

- Drug-exposed infants stand to benefit significantly from breastfeeding
  - Most illicit drugs are found in breastmilk with varying degrees of oral bioavailability
  - PCP and cocaine have been found in high concentrations in breastmilk leading to infant intoxication
  - Methadone concentrations in breastmilk are low, encourage to breastfeed regardless of maternal dose
    - Lack of healthcare support + misinformation are significant, modifiable barriers
  - Alcohol transfers easily, advise to wait 90-120m before breastfeeding or pump and dump during that period
  - Use caution recommending breastfeeding in chronic marijuana users

- Smoking appears independent risk factor for non-initiation and early cessation, encourage NRT (compatible with breastfeeding)

Summary on Perinatal Substance Use

- Substance use may effect the fetus directly or indirectly
  - Passage through the placenta vs poor maternal health habits/environmental conditions

- Symptoms/disorders associated with prenatal exposure may not present until adolescence or early adulthood
  - Epidemiology studies confounded by multiple covariates, few prospective studies

- Pregnancy, itself, presents motivation for cessation
  - Interventions must concentrate on cessation, and not abstinence, to have long-lasting effects
    - Screening tools should be used multiple times per pregnancy as rapport develops between patient and provider
  - Follow-up should continue into the postpartum period

- Idaho does NOT have state laws regarding mandatory reporting
  - 17 States consider substance use during pregnancy as child abuse
  - 3 States consider substance use as grounds for involuntary commitment to a mental health or substance use treatment facility
References

References

- Chen X et al. Long-acting cocaine hydrolase for addiction therapy. Proc Natl Acad Sci U S A. 2016 Jan 12;113(2):422-7