PREGNANCY, GENETICS, & WOMEN'S HEALTH

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ASAM Review Course: Pregnancy, Genetics, & Women's Health

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Learning Objectives

Interact with patients and professional colleagues so as to display professionalism in all activities, by demonstrating commitment to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behavior.

Identify their feelings and attitudes that promote or prevent therapeutic responses to their patients with substance use disorders.

Describe addictive disorders as developmental biopsychosocial disorders.

Implement evidence-based approaches to detecting substance use disorders.

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Learning Objectives

Conduct a biopsychosocial and developmental ambulatory assessment of an adult with a suspected SUD to match the patient to an appropriate level of care.

List the indications, contraindications and duration of treatment of evidence based pharmacotherapy for alcohol, tobacco, and opioid use disorders and refer patient to specialty care where appropriate.

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Presentation Outline

- Genetics and substance use disorder
- Gender differences in substance use disorder
- Pregnancy and the postpartum period
- Effects of substance use during pregnancy on the newborn
- Neonatal opioid withdrawal syndrome

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GENETICS AND SUBSTANCE USE DISORDER

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Three ways that genetics influences substance use disorder

Direct effect of genes on susceptibility to substance use disorder	Pharmacogenetics affects how drugs affect an individual	Epigenetics affects which genes are expressed

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Genetics of substance use disorder

- Nature vs nurture better phrased as nature and nurture for substance use disorder. A person's likelihood of developing substance use disorder is a result of a dynamic interaction between genes and the environment.[1]
- Heritabilities of SUD's range from 0.39 for hallucinogens to 0.72 for cocaine.

1. Genetics and Epigenetics of Addiction. in DrugFacts. https://www.drugabuse.gov/publications/drugfacts/genetics-epigenetics-addi
2. Bevilacqua and Goldman. Genes and Addictions. Clin Pharmacol Ther. 2009 APril; 85(4) pp 359-361

8

Twin studies – direct effect of genes

- Both the Swedish and Vietnam twin studies showed significantly higher concordance rates for substance use disorder in monozygotic twins than in dizygotic twins.[1,2]

1. Gelernter et Kranzler. Chapter 2. Genetics of Addiction in Galanter et al. Textbook of Substance Abuse Treatment. The American Psychiatric Publishing 2015 pp. 26-45
2. Bevilacqua and Goldman. Genes and Addictions. Clin Pharmacol Ther. 2009 APril; 85(4) pp 359-361

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Pharmacogenetics

- Both the ADH1 B2-His47 ARG allele of Alcohol Dehydrogenase 1B and ALDH-Glu487 Lys allele of Aldehyde Dehydrogenase 2 can cause flushing, nausea, and headache with alcohol, due to accumulation of acetaldehyde.[1]
  - More common in person of South Asian descent and those of Jewish ancestry.
  - Homozygotes nearly completely protected from alcoholism.

1. Zajicek and Karan. Pharmacokinetic and Pharmacodynamic Principles in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019. p. 97-98

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Pharmacogenetics of medication therapy of OUD

- The A118G SNP (single nucleotide polymorphism) of the opioid mu receptor (OPRM1) enhances the therapeutic response to naltrexone for alcohol dependence.[1]
  - A118G is also much more common in people with heroin use disorder.[2]
- Increased length of stay and increased need for pharmacotherapy in Neonatal Opioid Withdrawal Syndrome have recently been observed among neonates with variations in the A118G SNP in the mu opioid receptor OPRM1 gene and various SNP's in the COMT (Catechol-O-methyltransferase – enzyme that degrades dopamine, norepinephrine, and epinephrine.)[3]

1. Haile et al. Pharmacogenetic Treatments for Drug Addiction: Alcohol and Opiates, The American Journal of Drug and Alcohol Abuse, 34:4, 355-381
2. Ibid
3. Wachman et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of NAS. JAMA 2013;309(17):1821-1827

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Pharmacogenetics of medication therapy of OUD

- Methadone is metabolized in part by CYP2D6.
  - Ultrarapid metabolizers do not do well on methadone.[1]

1. Haile et al. Pharmacogenetic Treatments for Drug Addiction: Alcohol and Opiates, The American Journal of Drug and Alcohol Abuse, 34:4, 355-381

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Epigenetics

- Epigenetics is the study of epigenomes which are markers that turn genes on or off or express them more or less strongly.
  - Changes to the epigenomes can be passed down anywhere from 2-12 generations.
  - Environmental factors like diet, stress, and prenatal drug use can cause epigenetic changes which predispose to substance use disorder.

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Epigenetics

- Example of epigenetics is methylation of the -10 CpG site within the OPRM1 promoter region.
  - Passed from mother to baby
  - Babies with this epigenetic change were more likely to need treatment for neonatal opioid withdrawal syndrome.
  - Hypermethylation of this site may down-regulate the OPRM1 gene expression. This in turn leads to decreased levels of the mu-opioid receptor, which in turn leads to a need for more opioids to control NOWS.

Wachman EM, Hayes MJ, Lester BM, et al. Epigenetic variation in the mu-opioid receptor gene in infants with neonatal abstinence syndrome. *J Pediatr*. 2014;165(3):472–478. doi:10.1016/j.jpeds.2014.05.040

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GENDER DIFFERENCES IN SUBSTANCE USE DISORDER

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Gender differences and substance use disorder

- Men are more likely than women to use almost all types of illicit drugs.[1]
  - Women probably use prescription drugs at greater rates than men.[2]
  - Men are 1.9 times more likely to have drug dependence.[3]
- Men have higher rates of alcohol use, including binge drinking, than women, except for teens, where rates are similar.[4]

1. Substance Use in Women Research Report Sex and Gender Differences in Substance Use https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use Accessed 2/18/2021
2. Greenfield et al. Substance Abuse in Women. Psychiatr Clin Nort Am. 2010 June; 33(2): 339-355
3. Ibid
4. Substance Use in Women Research Report Sex and Gender Differences in Substance Use https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use Accessed 2/18/2021

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Gender differences and substance use disorder

- Women are more likely to be introduced to injection drug use by their male sexual partner, whereas men are more likely to be injected by a friend.[1]

1. Greenfield et al. Substance Abuse in Women. Psychiatr Clin Nort Am. 2010 June; 33(2): 339-355

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Gender differences and substance use disorder

- Women are more likely to use prescription opioids to self-medicate for anxiety or stress.[1] Men are more likely to use prescription opioids for experimentation or to get high.[2]
- Women are more likely to drink in response to stress and negative emotions whereas men are more like to drink to enhance positive emotions or conform to a group.[3]

1. Final Report: Opioid Use, Misuse, and Overdose in Women.. Office on Women's Health. July 19, 2017
2. Greenfield et al. Substance Abuse in Women. Psychiatr Clin Nort Am. 2010 June; 33(2): 339-355
3. Ibid

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Women and alcohol

- Women get drunker faster than men:
  - Decreased body weight[1]
  - Decreased alcohol dehydrogenase[2]
  - Decreased volume of water compartment distribution[3]
  - Less muscle than then men

1. Zweben. Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 p. 529
2. Ibid
3. Ibid

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Health risks for women with substance use disorder

- Women have "telescoped course" for alcohol use disorder.[1]
  - They develop pathologic effects of alcohol more rapidly.
- Women have a 50-100% higher death rate from alcohol use disorder, including deaths from suicide, alcohol-related accidents, heart disease, stroke, and liver damage.[2]

1. Zweben. Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine, Sixth Edition. Wolters Kluwer 2019 p. 529
2. Substance Use in Women Research Report Sex and Gender Differences in Substance Use https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use Accessed 2/18/2021

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CDC guidelines for risky drinking[1]

- Excessive drinking (or risky drinking or at risk drinking) is defined as the following:
  - Binge drinking, the most common form of excessive drinking, is defined as consuming
    - For women, 4 or more drinks during a single occasion.
    - For men, 5 or more drinks during a single occasion.
  - Heavy drinking is defined as consuming
    - For women, 8 or more drinks per week.
    - For men, 15 or more drinks per week.
- Most people who drink excessively are not alcoholics or alcohol dependent.
- Recent commentary by Lowik et al in the Journal of Addiction Medicine discussed whether adjustments are needed for these guidelines.

1. https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm accessed 2/17/2021
2. Lowik et al. **Where is the Science? A Critical Interrogation of How Sex and Gender are Used to Inform Low-Risk Alcohol Use Guidelines.** *J. Addict Med* Vol 14, No. 5, Sept/Oct 2020

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Incarceration and substance use disorder

- A population-based study showed that 22% of patients with substance use disorder had been incarcerated before.
- 10.6% of the general population reported a history of incarceration.

Tsai, J., Gu, X. Utilization of addiction treatment among U.S. adults with history of incarceration and substance use disorders. *Addict Sci Clin Pract* **14**, 9 (2019).

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Incarceration and substance use disorder

- Men with SUD were found to be more likely to have a history of incarceration as women with SUD.[1]
- Blacks and Latinos are far more likely to be incarcerated for drug law violations than whites, even though rates of drug use and drug selling are similar.[2]

1. Tsai, J., Gu, X. Utilization of addiction treatment among U.S. adults with history of incarceration and substance use disorders. *Addict Sci Clin Pract* **14**, 9 (2019).
2. http://www.drugpolicy.org/resource/drug-war-mass-incarceration-and-race-englishspanish Accessed 02/16/2021

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Women and violence and SUD

- Girls with a history of childhood sexual abuse are 3 times as likely to develop an addictive disorder as girls without that history.[1]
- One study showed lifetime intimate partner violence victimization was reported by 46.7% of women and 9.5% of men entering SUD treatment.

1. Zweben. Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 p. 532
2. Schneider et al. Violence and Victims, Volume 24, Number 6, 2009 744 © 2009 Prevalence and Correlates of Intimate Partner Violence Victimization Among Men and Women Entering Substance Use Disorder Treatment

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PREGNANCY AND SUBSTANCE USE DISORDER

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Definition of terms for providers not regularly doing obstetric care

- G = Gravida = total number of pregnancies
- P = Para = total number of deliveries
- XX weeks = weeks since last menstrual period or weeks since conception + 2
- Full-term = 37-41 weeks gestation
- IUGR = Intrauterine growth restriction = fetal weight by ultrasound < 10th percentile
- SGA = small for gestational age = weight of newborn baby < 10th percentile for gestational age

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Definition of terms for providers not regularly doing obstetric care

- Preterm labor = labor at < 37 weeks
- Preterm delivery = delivery at < 37 weeks
- Placental abruption = placenta pulls away from the wall of the uterus. Small abruptions can cause IUGR or preterm labor. Large abruptions can be fatal for mother and baby.

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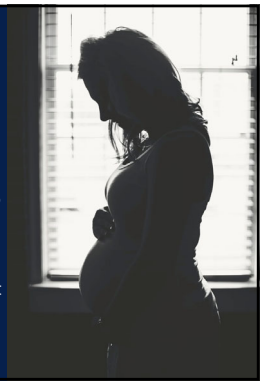
Case Study

33 yo G4P3 had been stable on buprenorphine-naloxone for 4 years. Presented to her buprenorphine provider for routine appointment and was discovered to be pregnant. Her buprenorphine provider did not give her a script because of this. She relapsed to heroin. She presented to our clinic at 25 weeks gestation, but because of transportation difficulties, she was unable to get restarted on buprenorphine and delivered a premature infant at 31 weeks. She restarted buprenorphine postpartum, and both she and baby did well.



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Case Study

22yo G1P0 presents @ 9 weeks gestation. Actively using heroin. Desperately wanted to keep this pregnancy and this child. Started on buprenorphine maintenance, did well. Child with no signs of Neonatal Opioid Withdrawal Syndrome at birth. Currently 7 years old, doing well.

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Substance use in pregnancy

- Use of alcohol, tobacco, and drugs during pregnancy is the leading preventable cause of mental, physical, and psychological impairments in children.
- Between 1998-2011, there was a 127% increase in opioid-dependent pregnant women presenting for delivery.[1]
- Opioid-dependent pregnant women have an unintended pregnancy rate of 86%.[2]

1. McCarthy et al. Opioid dependence and pregnancy: minimizing the stress on the fetal brain. American Journal of Obstetrics and Gynecology. 3 December 2016. pp 1-6
2. Wesver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 P. 1315

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Perinatal SBIRT: 4 Ps Plus

4Ps Plus:

Parents	Did either of your parents ever have a problem with alcohol or drugs?
Partner	Does your partner have a problem with alcohol or drugs?
Past	Have you ever had a problem with alcohol or drugs in the past?
Past 30 days alcohol	In the past month, have you drunk any or used any substances?

1. ACOG committee opinion 711, 2017
2. J Perinatol. 2005 Jun;25(6):368-74.

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- What are medical implications of substance use disorder with pregnancy?
- What is the significance of pregnancy for any substance use disorder?

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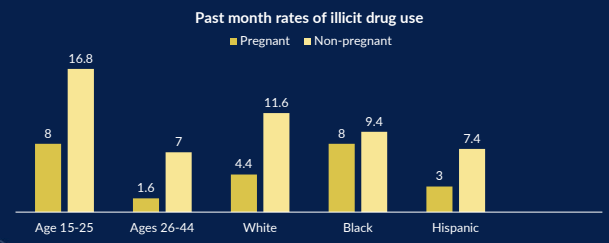
Percentages of past-month illicit drug use in pregnant and non-pregnant women



Helmbrecht et al. Management of Addiction Disorders in Pregnancy. *J Addict Med;* Vol 2, Number 1, March 2008, pp 1-16

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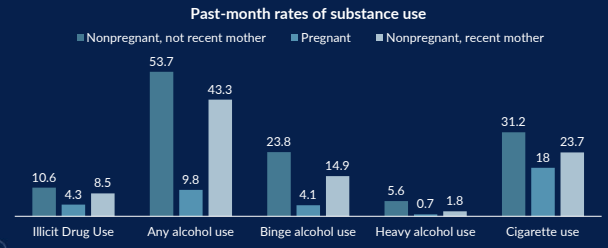
Percentages among women aged 15-44 years who reported past-month substance use by pregnancy and recent motherhood status



Helmbrecht et al. Management of Addiction Disorders in Pregnancy. *J Addict Med;* Vol 2, Number 1, March 2008, pp 1-16

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Birth defects with substances

- The drug with the most teratogenic potential is alcohol.[1]

1. Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 P 1317

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Fetal alcohol syndrome

- Evidence of growth restriction (prenatal and/or postnatal)
  - Height and/or weight <= 10th percentile
- Evidence of deficient brain growth and/or abnormal morphogenesis
  - Structural brain anomalies or head circumference <=10th percentile
- Characteristic pattern of minor facial anomalies
  - Short palpebral fissures, thin vermillion border upper lip, smooth philtrum

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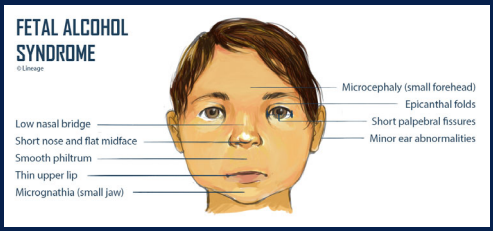
Fetal alcohol syndrome



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Fetal alcohol effects

- Incidence of fetal alcohol syndrome = 6-9/1000 children[1]
- Incidence of partial fetal alcohol syndrome = 11-17 per 1000 children[2]
- Incidence of fetal alcohol spectrum disorder = 24-48 per 1000 children[3]

1. Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 p. 1319

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Tobacco and pregnancy

- Neonates born to mothers who smoke weigh an average of 200 gm less than neonates born to mothers who don't smoke.[1]
- 22% of SUIDs (Sudden Unexpected infant deaths) can be directly attributed to maternal smoking during pregnancy.[2]

1. Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019P 1318
2. : Anderson TM, Lavista Ferres JM, Ren SY, et al. Maternal Smoking Before and During Pregnancy and the Risk of Sudden Unexpected Infant Death. Pediatrics. 2019; 143(4):e20183325

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Marijuana and pregnancy

- No teratogenic pattern to cannabis.[1]
- Recent meta-analyses have disagreed as to whether cannabis affects birthweight.[2,3,]
  - The meta-analysis that adjusted for tobacco and alcohol use did not show an effect.[2]
- There do seem to be neurodevelopmental deficits associated with cannabis use.[4]

1. Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019P 1325
2. Gunn JK et al. **Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis.** BMJ Open. 2016 Apr 5;6(4):e009986. doi: 10.1136/bmjopen-2015-009986.
3. Conner et al. Maternal Marijuana Use and Adverse Neonatal Outcomes: A Systematic Review and Meta-analysis. Obstet Gynecol. 2016 Oct;128(4):713-23. doi: 10.1097/AOG.0000000000001649.
4. Weaver et al. Ibid.

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Implications of opioid use disorder with pregnancy

- Medication: Both use and withdrawal have fetal effects. **Withdrawal effects usually considered more serious.**
  - Withdrawal causes a hyperadrenergic state which causes constriction of blood vessels in placenta. Exacerbated by cocaine and methamphetamine use. Can cause preterm labor and placental abruption.
  - Biggest direct effect of opioid use is Neonatal Opioid Withdrawal Syndrome at birth.

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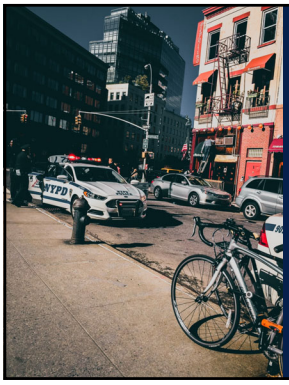

Case Study
Pregnancy and Substance Use Disorder

28 yo G5P4, on methadone maintenance, disappeared from care at about 20 weeks, returned at 38 weeks in labor. Stated she had been at a methadone clinic in another community, but urine was negative for methadone, + for opiates. Baby went into horrible withdrawal at birth, child protective services involved and took child. Mother was arrested when she and her cousin, who was foster mother, got in fight on OB floor.

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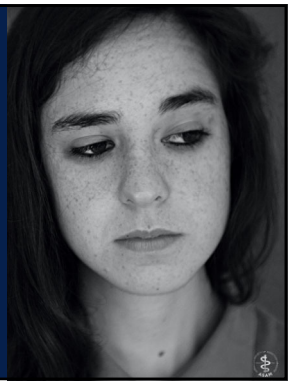
Case Study
Pregnancy and Substance Use Disorder

23 yo G2P1 presented using heroin. Started on buprenorphine with good response. Metabolite testing confirmed patient was taking medication. Incarcerated. Patient found with large quantities of methamphetamine and heroin and drug paraphernalia in her cell. Jail wished to stop buprenorphine. Told it needed to be continued. She was placed in solitary because of this.



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- What are psychosocial implications of substance use disorder with pregnancy?

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Implications of substance use disorder with pregnancy

- Co-occurring disorders
  - Depression.
    - Both substance use disorder and depression cause poor self-care.
  - Domestic violence
    - Second-leading cause of trauma-related death in pregnancy.

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Implications of substance use disorder with pregnancy

- Psychosocial:
  - Most mothers have a high motivation to change.
  - Lot of guilt/shame for many women
  - Legal implications around custody of baby and older children
  - Most substance-using pregnant women have very poor self-care behaviors. If they continue to use drugs, they are unlikely to take good care of themselves during the pregnancy.

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Implications of substance use disorder with pregnancy

- Psychosocial:
  - Often have history of childhood sexual abuse or physical abuse (with implications for parenting)
  - High incidence of PTSD
  - Most women who abuse drugs start using because their partners abuse drugs. If they are still with that partner, it can be difficult for them to quit unless he quits as well.

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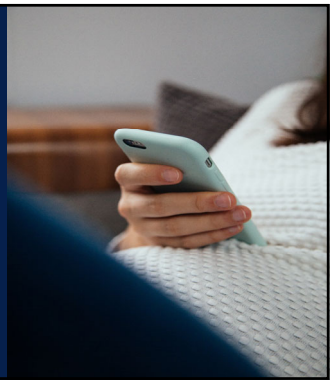
Comorbid Medical Conditions Case Study Pregnancy and Opioid Dependence

25 yo G2P1 presents at 26 weeks, stating, “I’m addicted to heroin.” Scared that she will lose baby to child protective services or have medical complications. She wants to get into treatment.



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- Is medication therapy an option for her?
- Which is better, buprenorphine or methadone?
- What about weaning off the heroin and using abstinence-based therapy?
- Does she need any special care for her pregnancy?

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Prenatal Care

- In a study in the Journal of Perinatology, it was found that women with illicit drug use and no prenatal care had the highest risk for prematurity, low-birth weight and small for gestational age infants. As prenatal care increased, risk for prematurity, low birth weight and small for gestational age babies dropped.[1]
- Women will often delay or not get prenatal care because of stigma and fear of consequences, including being reported to child protective services.[2]

1. El-Mohandes et al. Prenatal Care reduces the Imapce of Illicit Drug use on Perinatal Outcomes. Journal of Perinatology. 2003; 23:354-360
2. Bishop et al. Pregnant Women and Substance Use. Overview of Research and Policy in the United States. Bridging the Divide: A Project of the Jacobs Institute of Women's Health. February 2017

50

- Abstinence-based therapy is not recommended during pregnancy for anyone who is actively using opioids.[1]

1. Kampman and Jarvis. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. J Addict Med 2015;9 358-367

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Medication therapy and pregnancy

- Medication therapy for opioid use disorder (MOUD) is standard of care for pregnancy

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Medication therapy and pregnancy

- Medication therapy can be done with either methadone or buprenorphine.
  - Methadone has been used longer, but most providers prefer to start with buprenorphine if available.
- Data regarding naltrexone is limited, but it is probably safe to continue in pregnancy if patient wishes. It should not be started in pregnancy.

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Buprenorphine vs methadone in Pregnancy

- 2010 NEJM study showed significantly less Neonatal Opioid Withdrawal Syndrome in buprenorphine group than the methadone group[1]
  - Babies exposed to buprenorphine required 89% less morphine, had a 43% shorter hospital stay, and shorter duration of treatment than babies exposed to methadone[1]
- 2016 UC-Davis study split dosage of methadone for all pregnant women. It showed much better outcomes, with rate of Neonatal Opioid Withdrawal Syndrome = 29%.[2]

1. Jones, H. et al. Neonatal Opioid Withdrawal Syndrome after Methadone or Buprenorphine Exposure. *NEJM*; Vol 363, 12/9/10 pp 2320-31
2. McCarthy, J et al. The Effect of Methadone Dose Regimen on Neonatal Opioid Withdrawal Syndrome. *J Addict Med*; Vol 9, Number 2, March/April 2015. pp 105-110.

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Differences in treating with buprenorphine and methadone in pregnancy

- Doses may need to be increased because of increased metabolism, especially in the third trimester.
- If at all possible, therapy should not be interrupted.
- Buprenorphine should be started in a monitored environment, preferably a hospital for women with a viable fetus.
- Buprenorphine is generally recommended to be the monoproduct, although a recent study showed combination product to be safe[1].

1. Mullins et al. Buprenorphine and Naloxone versus Buprenorphine for Opioid Use Disorder in Pregnancy: A Cohort Study *J Addict Med* Volume 14, Number 3, May/June 2020

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- What about medically monitored withdrawal?

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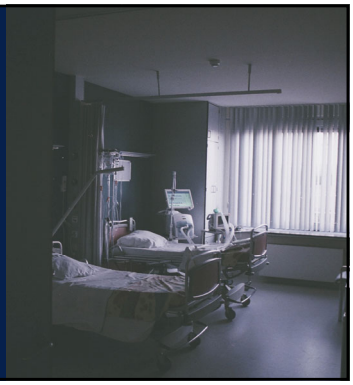
Case Study

Patient is a 36 yo G2P1 at 36 weeks. Wanted to start on buprenorphine. Told to stop heroin 12 hours before coming into hospital to start. She stopped 48 hours before. Came into hospital in florid withdrawal. Noted to be having contractions. Cervix was completely dilated on exam. Delivered 30 minutes later.



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Medically Monitored withdrawal

- Most studies show a high rate of relapse to opioid[1,2]
  - Rates range from 17-96%[3,4,5]
  - Relapse rate is lower on medication therapy[6]
- No study of medically monitored withdrawal has examined maternal outcomes postpartum[7]

1. Dashe et al. Opioid detoxification in pregnancy. Obstetrics and Gynecology, Volume 92, Issue 5, November 1998, pp 854-858
2. Bell et al. Detoxification from opiate drugs during pregnancy. Am J Obstet Gynecol 2016;215:374.e1-6
3. Dashe et al. pp. 854-858
4. Jones et al. Medically Assisted Withdrawal (Detoxification): Considering the Mother-Infant Dyad. J Addict Med 2017 DOI 10.1097
5. Bell et al. Ibid.
6. Jones et al. Ibid
7. Jones et al. Ibid

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- The previous patient has made it to term and is about to go into labor.
- Do you need to do anything special to manage her labor?
- What can you expect for the baby?
- Can she breast-feed?
- What can she expect post-partum?

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Labor and delivery

- Method of delivery should be based solely on obstetric considerations.
- Epidural is preferred method of pain relief.
- If you use opioids, you need to use a full agonist with strong binding potential, or you risk making pain relief less.
  - Fentanyl is preferred agent.

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Post-partum mothers and substance use disorder

- High risk of relapse. Encourage them to continue with recovery behaviors and medication.
- Often, do not have good parenting skills. Consider home nursing, parenting classes.
- May have a more fussy baby than average – need a lot of support.

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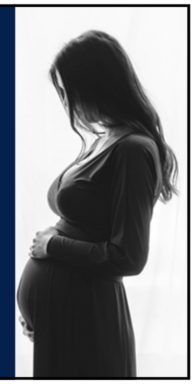
Comorbid Medical Conditions Case Study: Pregnancy and Opioid Dependence

34 yo G2P1 had been on buprenorphine-naloxone for heroin use disorder. She moved away and got pregnant and weaned herself off the buprenorphine. Moved back and declined to restart buprenorphine because "I am not going to ever go back to drugs." NSVD of healthy baby with negative urine drug screens throughout pregnancy. Died of an overdose about 1 year post-partum.



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Maternal mortality and opioid use disorder

Studies from Maryland, Tennessee, Colorado, Utah, Ohio, and Massachusetts have found that postpartum overdose is one of the top causes of maternal mortality, causing 15-33% of deaths.

1. https://phpa.health.maryland.gov/mch/Documents/Health-General%20Article,%20%C2%A713-1207,%20Annotated%20Code%20of%20Maryland%20-%202019%20Annual%20Report%20%E2%80%93%20Maryland%20Maternal%20Mortality%20Review.pdf Accessed 2/18/2021
2. Tennessee Maternal Mortality Review of 2Maryland Maternal Mortality Review. 2014 Annual Report. MD Dept of Health and Mental Hygiene. Prevention and Health Promotion Administration.
3. Metz et al. Maternal Deaths from Suicide and Overdose in Colorado, 2004-2012. Ob Gyn. Vol 128. No. 6. December 2016. pp 1233-1240
4. Smid et al. Pregnancy-Associated Death in Utah: Contribution of Drug-Induced Deaths. Obstet Gynecol. 2019 Jun; 133(6): 1131-1140
5. Hall et al. Pregnancy-Associated Mortality Due to Accidental Drug Overdose and Suicide in Ohio, 2009-2018. Obstetrics and Gynecology. Vol 136, No 4 October 2020
6. Schiff et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. Obstet Gynecol. 2018

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Maternal mortality and opioid use disorder

- Suicide is also a substantial contributor to postpartum mortality.[1]
- Risk factors for postpartum opioid overdose and postpartum suicide have significant overlap.[2]
- Three of the most common include depression, intimate partner violence, and substance use disorder.
- Screen for depression postpartum. Use Edinburgh Postpartum Depression Screen or another tool.

1. Campbell et al. Pregnancy- Associated Deaths from Homicide, Suicide, and Drug Overdose: Review of Research and the Intersection with Intimate Partner Violence. *Journal of Women's Health*. Volume 30, Number 2, 2021.
2. Mangla et al. Maternal self-harm deaths: an unrecognized and preventable outcome. American Journal of Obstetrics and Gynecology. October 2019.

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Increased maternal mortality continued for many years after delivery in 2019 study

Mothers in Ontario and England with babies who had neonatal abstinence syndrome have a mortality rate that is over ten times as high as mothers who did not have an affected baby.

Roughly 1 in 20 mothers died over the next decade.

Top cause of death was unintentional injuries, but there were also high rates of murder and suicide, drug-related deaths, and unavoidable deaths.

Guttmann A et al. Long-term mortality in mothers of infants with neonatal abstinence syndrome: A population-based parallel-cohort study in England and Ontario, Canada. PLoS Med 16(11): e1002974. November 26, 2019.

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NEONATAL OPIOID WITHDRAWAL SYNDROME

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Neonatal Opioid Withdrawal Syndrome definition

- Neonatal Opioid Withdrawal Syndrome = physical withdrawal.
- Neonatal Opioid Withdrawal Syndrome baby is ≠ addicted to drugs.

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Social determinants of neonatal opioid withdrawal syndrome

Long-term unemployment and a shortage of mental health clinicians are associated with higher rates of neonatal abstinence syndrome on a county level.[1]

Poverty is also associated with excess length of stay for NOWS.[2]

States with potentially punitive policies toward pregnant women around substance use (policies considering it child abuse or neglect) showed a significant increase in rates of NOWS in the years after the policies were put in place.[3]

1. Patrick, Stephen et al. Association Among County-Level Economic Factors, Clinician Supply, Metropolitan or Rural Location, and Neonatal Abstinence Syndrome. JAMA. 2019; 321(4): 385-393.
2. Vesoulis et al. Poverty and Excess Length of Hospital Stay in Neonatal Opioid Withdrawal Syndrome. J. Addict Med. Volume 14, Number 2, March/April 2020
3. Flaherty, Laura et al. Association of Punitive and Reporting State Policies Related to Substance Use in Pregnancy With Rates of Neonatal Abstinence Syndrome. JAMA Network Open. 2019; 2(11): e1914078.

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Neonatal Opioid Withdrawal Syndrome symptoms (for a baby withdrawing from opiates)

Gastrointestinal symptoms: emesis, diarrhea, poor feeding

Autonomic over-reactivity: sneezing, rhinorrhea, yawning, tachycardia, increased metabolic rate

CNS symptoms: Irritability, increased tone, high-pitched cry, hypersensitivity to stimuli, seizures if untreated

Poor weight gain due to all of the above

Measured using Finnegan score

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Most important symptoms

- Can baby eat?
  - Can baby take in at least an ounce per feed
- Can baby sleep?
  - Can baby sleep undisturbed for at least an hour?
- Can baby be consoled?
  - Can crying baby be consoled in 10 minutes or less?
- Babies who were measured on these criteria rather than the Finnegan or similar scales were given significantly less morphine with decreased length of stay and no adverse outcomes.[1]

1. Grossman et al. A Novel Approach to Assessing Infants with Neonatal Opioid Withdrawal Syndrome Hospital Pediatrics Volume 8, Issue 1, January 2018, pp 1-6

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Neonatal Opioid Withdrawal Syndrome

- Neonatal Opioid Withdrawal Syndrome is highly treatable if diagnosed early, limited in duration, and, as far as we know, has limited long-term effects compared to the effects of untreated opioid use disorder.
- We should never use the possibility of NOWS to justify not properly treating opioid use disorder.
- We should also make sure that all pregnant women who are under treatment with medication facing the possibility of a baby with NOWS understand that they are doing the best possible thing for their baby.

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Non-pharmacologic treatment of neonatal opioid withdrawal syndrome

- Small and frequent feeds. Frequent burping.[1]
- Quiet, dim light. Soft slow manner. Swaddling.[2]
- Skin-to-skin. Family involvement with rooming in.[3]
- Prenatal education about neonatal opioid withdrawal syndrome.[4]
- Frequent feeds and high calorie formulas may help with nutritional needs.[5]

1. Vekez et Jansson. The Opioid Dependent Mother and Newborn Dyad: Nonpharmacologic Care. J. Addict Med. 2008;2 113-120
2. Ibid
3. Ibid
4. Holmes et al. Rooming-In to Treat Neonatal Abstinence Syndrome: Improved Family-Centered Care at Lower Cost. Pediatrics 1026; pp
5. Kocherlota. Neonatal Abstinence Syndrome. Pediatrics. Volume 134, Number 2, August 2014. pp e547-e561

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Non-pharmacologic treatment of Neonatal Opioid Withdrawal Syndrome

- Dartmouth study showed use of non-pharmacologic treatments decreased percentage of babies needing treatment with morphine from 46% to 27%. Length of stay decreased from 16.9 days to 12.3 days. Average hospital cost per infant decreased from $19,737 to $8,735. No adverse effects[1]
- Yale Study showed the proportion of methadone exposed-infants treated with morphine decrease from 98% to 14% with institution of non-pharmacologic care and some changes in way medication was dosed. Hospital costs decreased from $44,824 to $10,289. Average length of stay decreased from 22.4 to 5.9 days.[2]

1. Holmes et al. Rooming-In to Treat Neonatal Opioid Withdrawal Syndrome: Improved Family-Centered Care at Lower Cost. Pediatrics 2016; pp 2015-2029
2. Grossman et al. An Initiative to Improve the Quality of Care of Infants with Neonatal Opioid Withdrawal Syndrome. Pediatrics 2017;139(6)

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Breastfeeding

- The Academy of Breastfeeding Medicine, the American Academy of Pediatrics, the American College of OB-GYN, the Substance Abuse and Mental Health Services Administration, and the American Society for Addiction Medicine recommend breastfeeding for women with substance use disorder who are in a treatment program and have had negative drug screens for 2 months prior to delivery.[1,2,3,4,5]
  - This includes women on MOUD.

1. Jansson, L. et al, **Methadone Maintenance and Breastfeeding in the Neonatal Period** PEDIATRICS Vol. 121 No. 1 January 2008, pp. 106-114
2. Reece-Stretman et al. **ABM Clinical Protocol #21: Guidelines for Breastfeeding and Substance use or Substance Use Disorder, Revised 2015 Breastfeeding Medicine:** Vol 10, November 3, 2015, pp 135-141
3. Substance Use, Misuse, and Use Disorders During and Following Pregnancy, with an Emphasis on Opioids. ASAM Policy Statement. January 18, 2017
4. Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants. SAMHSA. HHS Publication No. (SMA) 18-5054
5. ACOG Committee Opinion. Opioid Use and Opioid Use Disorder in Pregnancy. Number 711. August 2017.

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Long-term effects on baby of maternal methadone and buprenorphine use

- Very hard to control for other factors, such as other drug use, poor socioeconomic status, and inadequate prenatal care
- Infants born to mothers who received methadone or buprenorphine were found as toddlers to have no more problems than those from a sample without SUD[1]
- Neonatal outcome is improved if mothers get on methadone early in pregnancy or even before pregnancy.[2]

1. Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants. SAMHSA. HHS Publication No. (SMA) 18-5054
2. Logan et al. Neonatal Abstinence Syndrome: Treatment and Pediatric Outcomes. Clin Obstet Gynecol 2013 Mar; 56(1). Pp 186-192

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Child protective services and mental health

Study in Manitoba showed that losing custody of a child to child protective services is associated with significantly worse maternal mental health outcomes than experiencing the death of a child

Risk of depression was 1.90 times greater for women who had lost a child to child protective services.

Risk of substance use was 8.54 times greater for women who had lost a child to child protective services.

Wall-Wieler, Elizabeth et al. Maternal Mental Health after Custody Loss and Death of a Child: A Retrospective Cohort Study Using Linkable Administrative Data. The Canadian Journal of Psychiatry. 2018, Vol. 63(5) 322-328.

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Comprehensive addiction and recovery act

CARA requires states to identify and report on the following:

- Number of substance-exposed infants born
- Number of substance-exposed infants for whom a Plan of Care was created
- Number of infants with a Plan of Care for whom referrals were made to appropriate services, including services for affected family members or caregivers

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To Call Child Protective Services or not

- Know your state's laws
- Guttmacher Institute has a summary of many but not all state's laws:
  - https://www.guttmacher.org/state-policy/explore/substance-use-during-pregnancy
- Jacobs Institute of Women's Health *Bridging the Divide:* Pregnant Women and Substance Abuse also has information

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To Call Child Protective Services or not

- Discuss child protective service involvement during pregnancy
  - What will trigger a referral
  - What will likely happen with a referral
- Discuss with your patient what to do if a referral is made:
  - Be honest with child protective services
  - Have a plan for SUD treatment
  - Have a plan to ensure the baby is safe

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Take home messages

There is a substantial genetic component to substance use disorder.	Women are less likely than men to use drugs and alcohol but have worse outcomes when they do	Alcohol and tobacco are the most dangerous drugs for the fetus in pregnancy.
Medication treatment is recommended for opioid use disorder in pregnancy.	The postpartum period and after is a high risk time for relapse and death in women with SUD	Use non-medical treatments first for neonatal opioid withdrawal syndrome.

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Which of the following is true regarding gender differences with respect to substance use disorder?

A. Men are less likely to use illicit drugs than women are
B. Women are more likely to use drugs to celebrate, whereas men are more likely to use to cope with physical or emotional pain
C. Women will suffer adverse effects from their use of similar levels of alcohol much sooner than men will
D. Women with substance use disorder are more likely to have a history of incarceration than men are

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Which of the following is correct about opioid use disorder and pregnancy?

A. The highest risk time for relapse is postpartum
B. Medically-assisted withdrawal should be done during the second trimester to reduce the risk of neonatal opioid withdrawal syndrome
C. C-section is recommended for anyone actively using heroin
D. There is a high risk of congenital anomalies with opioid use

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Which of the following is an example of an epigenetic phenomenon?

A. Children in a household with high levels of alcohol consumption are more likely to drink alcoholPrefrontal Cortex
B. Children in a high-stress environment are more likely to have certain genes expressed, some of which will predispose them to substance use disorder
C. Some alleles of the ADH2 gene will cause flushing and nausea with alcohol ingestion, and thus are protective against alcohol use disorder
D. People who are ultra rapid metabolizers of methadone don't do well on it.

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