# Pregnancy, Genetics, & Womens' Health

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ASAM

# The ASAM Review Course of Addiction Medicine

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## Financial Disclosures

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# Learning Objectives

**Describe** genetic and gender differences impacting the assessment and treatment of addiction in women and list evidence-based treatment strategies for pregnant patients and newborns.

# 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

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# 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 people 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

# 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

# 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.



John Cloud. Why Your DNA Isn't Your Destiny. *Time.* 1/6/2010

# Gender Differences in Substance Use Disorder

# 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

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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

# Women and Alcohol

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

# Health Risks For Women with Substance Use Disorder

- Women have a "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).

# Incarceration And Substance Use Disorder

- Men with SUD were found to be more likely to have a history of incarceration than 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, Violence, and SUD

- Women with a history of childhood sexual abuse are three times as likely to develop an addictive disorder as women 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

# 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 < 10$^{th}$ percentile
- SGA = small for gestational age = weight of newborn baby < 10$^{th}$ percentile for gestational age

# 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.

# Case Study

33 yo G4P3 had been stable on buprenorphine-naloxone for four 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 at 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 seven 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]
  - Please provide or refer for contraception if you are treating female patients.

[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]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. 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 | In the past month, have you drunk any alcohol or used any substances? |

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

1. What are medical implications of substance use disorder with pregnancy?

2. What is the significance of pregnancy for any substance use disorder?

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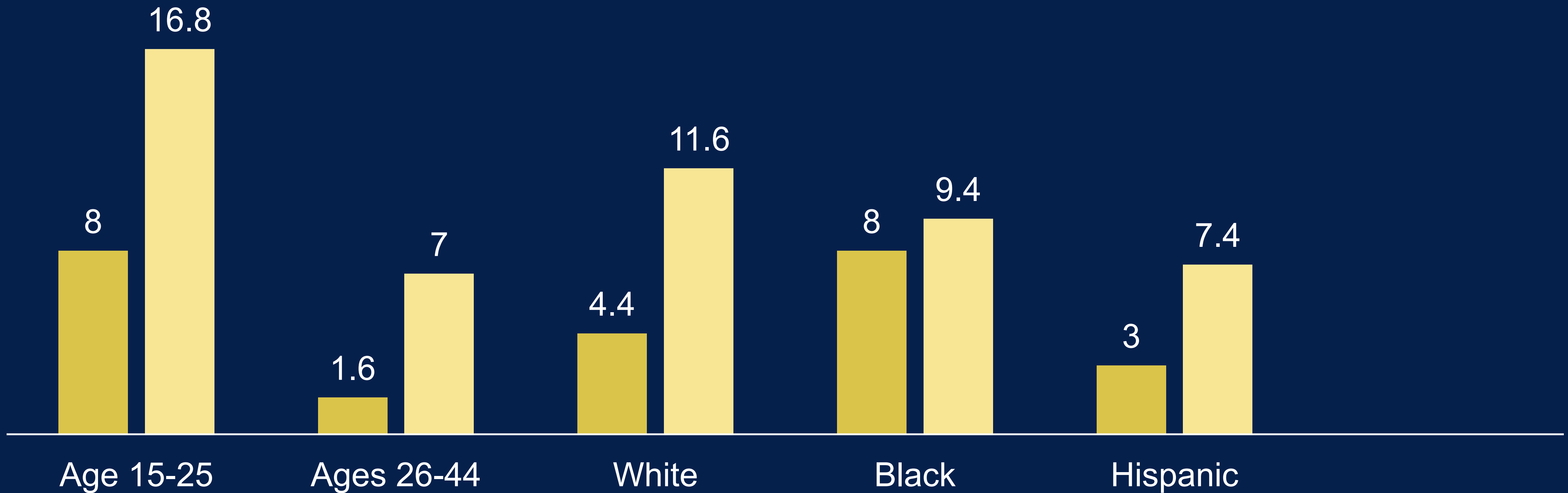
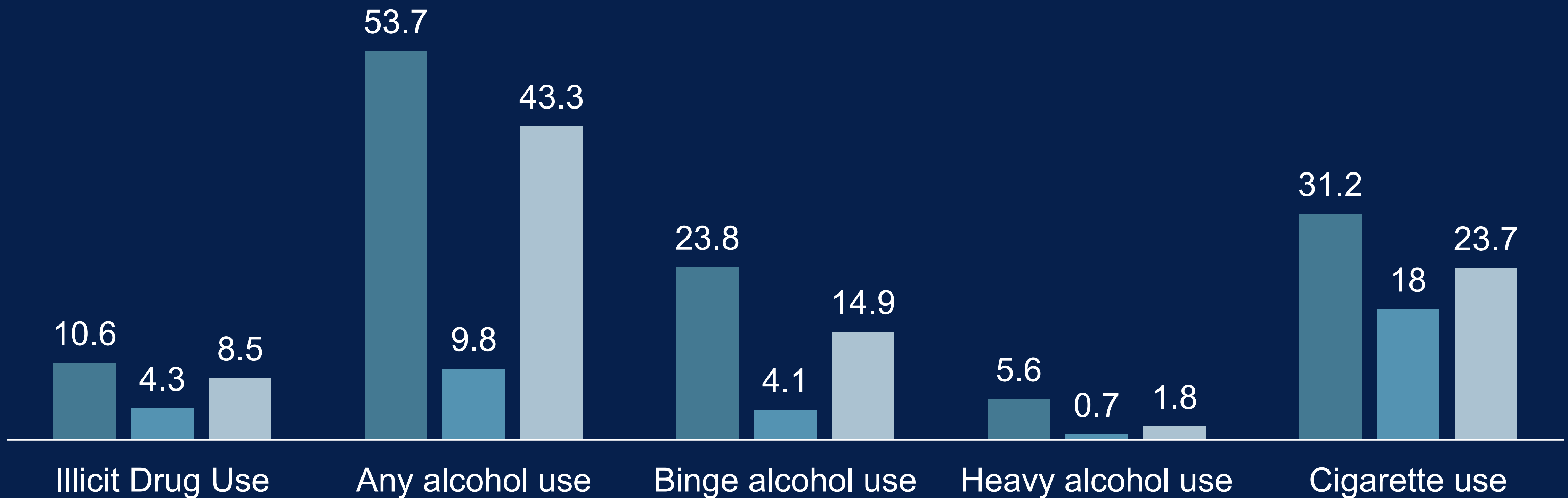
# Percentages Of Past-month Illicit Drug Use In Pregnant And Non-pregnant Women




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

# 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

# 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 and positive 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.

# 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.

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

# 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

# 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.

# 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 use drugs. If they are still with that partner, it can be difficult for them to quit unless he quits as well.

# 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 Impact 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

# Effects of Specific Substances on Pregnancy

# 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 <= 10$^{th}$ percentile
- Evidence of deficient brain growth and/or abnormal morphogenesis
  - Structural brain anomalies or head circumference <=10$^{th}$ percentile
- Characteristic pattern of minor facial anomalies
  - Short palpebral fissures, thin vermillion border upper lip, smooth philtrum

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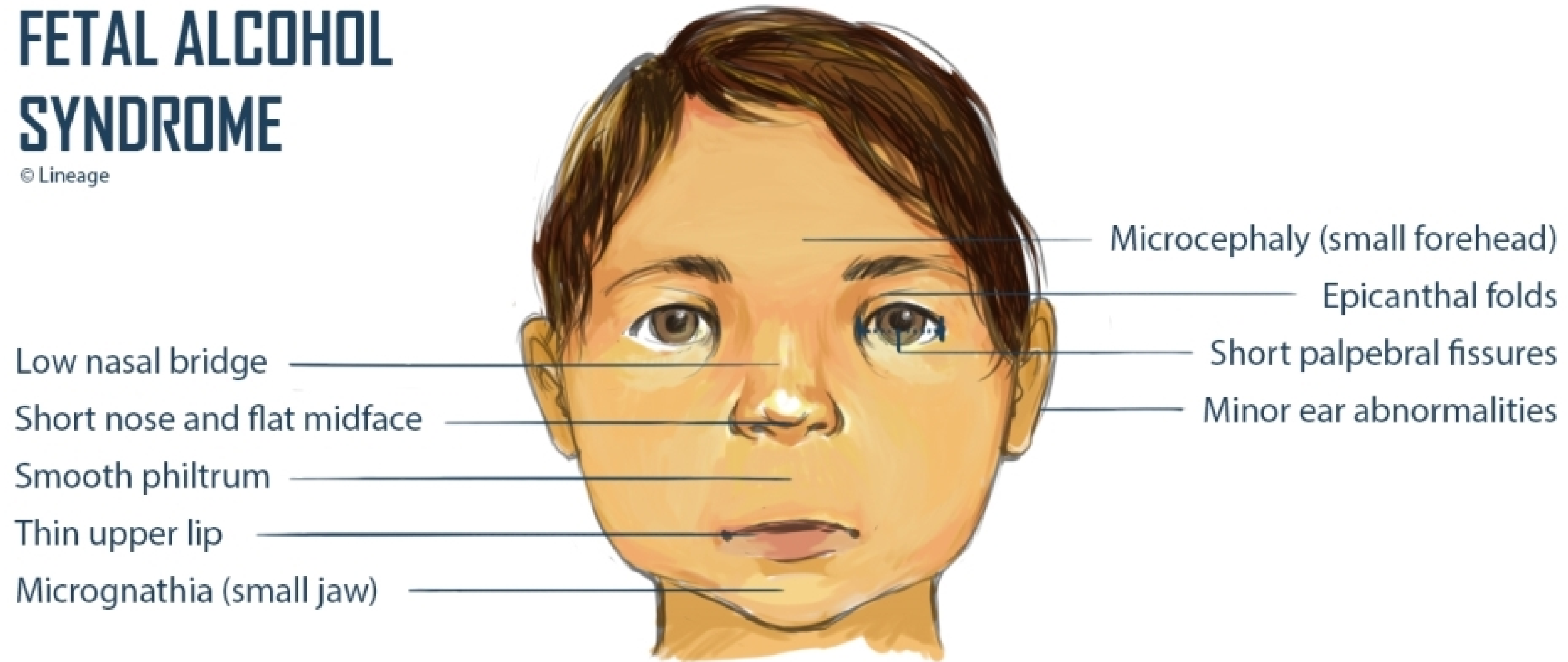
# Fetal Alcohol Syndrome



# 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

# Cannabis and Pregnancy

- Difficult to get definitive answers on effects:
  - Women often using other substances, especially alcohol and tobacco
  - Psychosocial variables, such as income, age, and education, vary
  - Pre-existing conditions, such as ADHD or anxiety
  - Many studies done before level of THC was as high as now
- Cannabis use is common – the prevalence of self-reported marijuana use is 2-5%, and it increased from 2.37% in 2002 to 3.85% in the 2014 NSDUH.[1]
  - One study showed 2.6% use by self-report, 22.4% by umbilical blood sampling.[2]

1. Thompson R, DeJong K, Lo J. **Marijuana Use in Pregnancy: A Review**. *Obstet Gynecol Surv*. 2019 Jul;74(7):415-428
2. Nashed et al. **Cannabinoid Exposure: Emerging Evidence of Physiological and Neuropsychiatric Abnormalities** *Frontiers in Psychiatry*. 11/2021

# Cannabis and Pregnancy

- Most common reasons to use cannabis in pregnancy are morning sickness and to manage anxiety/depression
  - Cannabis can lead to cannabis hyperemesis syndrome.[1]
- Data is mixed on effect of cannabis on pregnancy.
  - Studies have given varied results on effect on birthweight[2.3], birth defects[4], and other outcomes.
  - There does seem to be a pattern of neurobehavioral effects on the fetus, with hyperactivity and sleep problems in toddlers, ADHD in pre-teens, and emotional dysregulation in adolescents.[5,6,7]


1. Badowski S, Smith G. Cannabis use during pregnancy and postpartum. *Can Fam Physician*. 2020;66(2):98-103.
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. 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
5. Thompson R, DeJong K, Lo J. **Marijuana Use in Pregnancy: A Review**. *Obstet Gynecol Surv*. 2019 Jul;74(7):415-428
6. Nashed et al. **Cannabinoid Exposure: Emerging Evidence of Physiological and Neuropsychiatric Abnormalities** *Frontiers in Psychiatry*. 11/2021
7. Roncero et al. **Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review** . *Reprod Health*. 2020;17(1):25. 2020 Feb 17.

# Cannabis And Pregnancy – What We Need To Tell Our Patients

- Pregnant women complain about hearing mixed messages from healthcare providers. They also state that want more research on the safety and effects of cannabis with pregnancy.[1]
- There is no recognized "safe" amount of marijuana with pregnancy.
  - Although marijuana hasn't been found definitively to be dangerous, it has also most definitely not been found to be safe.
- There is very likely a risk of long-term neurocognitive effects.
- While it may help with morning sickness, it can lead to cannabinoid hyperemesis syndrome, which is way worse, and there are better treatments.

Barbosa-Leiker et al. Daily Cannabis Use During Pregnancy and Postpartum in a State With Legalized Recreational Cannabis, *Journal of Addiction Medicine*: November/December 2020 - Volume 14 - Issue 6 - p 467-474

# Stimulant Use and Pregnancy

- Methamphetamine[1] and cocaine[2] use are associated with the following:
  - Preterm delivery
  - Low birth weight
  - Small for gestational age infants

1. Kalaitzopoulos et al. Effect of Methamphetamine Hydrochloride on Pregnancy Outcome: A Systematic Review and Meta-analysis, *Journal of Addiction Medicine*: May/June 2018 - Volume 12 - Issue 3 - p 220-226
2. Smid MC et al. Stimulant Use in Pregnancy: An Under-recognized Epidemic Among Pregnant Women. *Clin Obstet Gynecol*. 2019;62(1):168-184.

# 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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# 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.

1. Is medication therapy an option for her?
2. Which is better, buprenorphine or methadone?
3. What about weaning off the heroin and using abstinence-based therapy?

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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

# 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]

[1] Jones, H. et al. Neonatal Opioid Withdrawal Syndrome after Methadone or Buprenorphine Exposure. *NEJM*. Vol 363, 12/9/10 pp 2320-31.

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# Buprenorphine vs. Methadone in Pregnancy

- Buprenorphine vs buprenorphine-naloxone
  - ASAM: "While the evidence on the safety and efficacy of naloxone in pregnant women remains limited, the combination buprenorphine/naloxone product is frequently used and the consensus of the guideline committee is that the combination product is safe and effective for this population."[1]
  - CDC: Combination pills containing both buprenorphine and naloxone are not recommended for treatment of OUD in pregnant women due to limited evidence at this time.[2]
  - SAMHSA: "Positions are evolving on using the combination product (buprenorphine/naloxone) throughout the pregnancy, rather than transitioning the pregnant woman to the buprenorphine-only product for the duration of her pregnancy. …Evidence is now building that newborn outcomes are not negatively affected by using the combination product during gestation and that pregnant women may not need to transition to the buprenorphine-only product during pregnancy to protect the fetus …Pregnant women and their healthcare professionals should make a decision with regard to the use of the buprenorphine/naloxone combination product in the context of pregnancy based on the benefit vs. the risk to the dyad."


1. The ASAM NATIONAL PRACTICE GUIDELINE For the Treatment of Opioid Use Disorder 2020 Focused Update
2. https://www.cdc.gov/pregnancy/opioids/treatment.html Accessed 3/36/2022
3. Substance Abuse and Mental Health Services Administration. Clinical Guidance for Treating Pregnant and Parenting Women With Opioid Use Disorder and Their Infants. HHS Publication No. (SMA) 18-5054. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.

# Buprenorphine and Pregnancy

- Does buprenorphine need to be started in a monitored environment?
  - ASAM: "Hospitalization during initiation of treatment with buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester."[1]
  - SAMHSA: "Many clinics now offer induction to buprenorphine as an outpatient service and sometimes as partial home induction. Partial home induction for pregnant women lacks sufficient evidence at this time."[2]
  - Recent study showed no cases of precipitated withdrawal in the home induction group and one in the observed induction group with successful induction onto buprenorphine for all.[3]


1. The ASAM NATIONAL PRACTICE GUIDELINE For the Treatment of Opioid Use Disorder 2020 Focused Update
2. Substance Abuse and Mental Health Services Administration. Clinical Guidance for Treating Pregnant and Parenting Women With Opioid Use Disorder and Their Infants. HHS Publication No. (SMA) 18-5054. Rockville ,MD: Substance Abuse and Mental Health Services Administration, 2018.
3. Kelly JC et al. **Home Induction of Buprenorphine for Treatment of Opioid Use Disorder in Pregnancy.** *Obstet Gynecol.* 2021 Oct 1;138(4):655-659.

# Access To Buprenorphine While Pregnant

- A 2020 study of obstetricians showed that only a third of obstetricians always recommend MOUD and a fourth never recommend it.[1]
- MOUD providers are far less likely to accept pregnant patients than non-pregnant patients.[2]
  - Methadone 97% vs 91%
  - Buprenorphine 83% vs 51%


1. Ko, J.Y., Tong, V.T., Haight, S.C. *et al.* Obstetrician–gynecologists' practice patterns related to opioid use during pregnancy and postpartum—United States, 2017. *J Perinatol* **40,** 412–421 (2020).
2. Stephen W. Patrick et al. (2018): Barriers to accessing treatment for pregnant women with opioid use disorder in Appalachian states, Substance Abuse

# Morning Sickness and Methadone

- Both ondansetron and methadone cause QT prolongation, so use other treatments first.
- Lifestyle changes:
  - Small frequent meals
  - Avoid fluids with meals
  - Eat something before getting out of bed
  - Popsicles
- Ginger
- Pyridoxine, 10 mg + Doxylamine, 10mg tid

# What about medically monitored withdrawal?

# 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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1. The previous patient has made it to term and is about to go into labor.
2. Do you need to do anything special to manage her labor?
3. What can you expect for the baby?
4. Can she breastfeed?
5. What can she expect post-partum?

# 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.

# 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 fussier 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, 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 one 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

[5]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

# Neonatal Opioid Withdrawal Syndrome Definition

- Neonatal Opioid Withdrawal Syndrome = physical withdrawal.

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

# Clinical Definition of Opioid Withdrawal in the Neonate from The AAP

- Presence of clinical elements 1 and 2
- **(1) In utero exposure** to opioids with or without other psychotropic substances (recommended to be collected via confidential maternal self-report; toxicology testing also acceptable with maternal informed consent)
- **(2)Clinical signs** characteristic of substance withdrawal; any 2 of the following 5 signs qualify:
  - Excessive crying (easily irritable)
  - Fragmented sleep (<2-3 h after feeding)
  - Tremors (disturbed or undisturbed)
  - Increased muscle tone (stiff muscles)
  - Gastrointestinal dysfunction (hyperphagia, poor feeding, feeding intolerance, loose or watery stools)

Jilani et al. Standardizing the Clinical Definition of Opioid Withdrawal in the Neonate. *The Journal of Pediatrics.* September/October 2020 - Volume 14 - Issue 5

# 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

- Non-pharmacologic treatment includes the following:
  - Small, frequent feeds.
  - Quiet, dim light.
  - Swaddling or skin-to-skin.
  - Prenatal education for parents.
- Studies from Dartmouth[1] and Yale[2] showed substantial improvements in cost and length of stay using non-pharmacologic treatment.

[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(60)

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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.

# Child Protective Services and Mental Health

**A 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

# To Call Child Protective Services or not

- Know your state's laws
- Child Welfare Information Gateway has a page that will let you look up your state's laws:
- https://www.childwelfare.gov/topics/systemwide/laws-policies/state/
- Know your local hospitals' policies.

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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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