From Seed to Bud: The Impact of Cannabis Use Across the Lifespan

32nd Annual Internal Medicine Review

PRESENTED BY: Jamie Lo, MD, MCR, and Jasper Bash, MD
DATE: April 10th, 2024

Disclosures

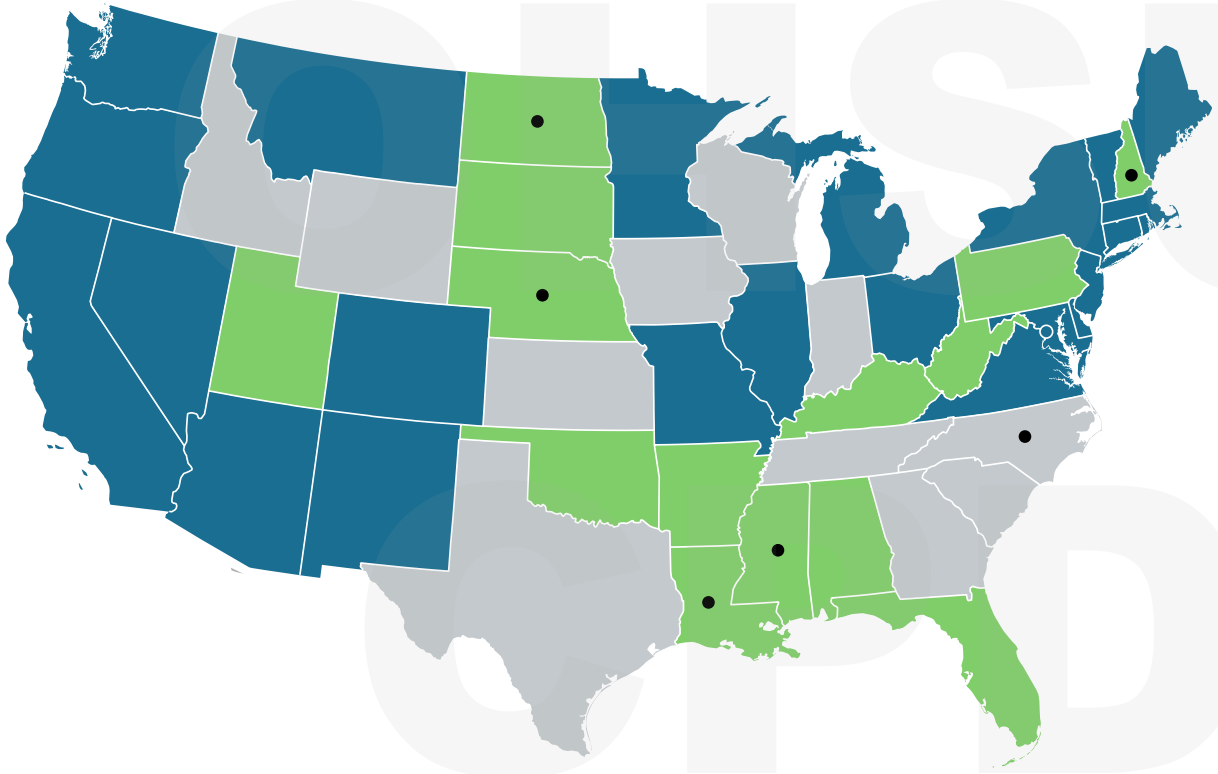
No financial disclosures

Reference: https://lcb.wa.gov/education/growing_cannabis_at_home

Objectives

- Review the modern trends of cannabis composition and use
- Define the current recommendations regarding cannabis use in those attempting to conceive
- Discuss the risks of cannabis use relating to sexual function and menopause
- Provide tools and data for counselling patients regarding the potential impacts of paternal or maternal cannabis use and offspring outcomes

Cannabis Legalization



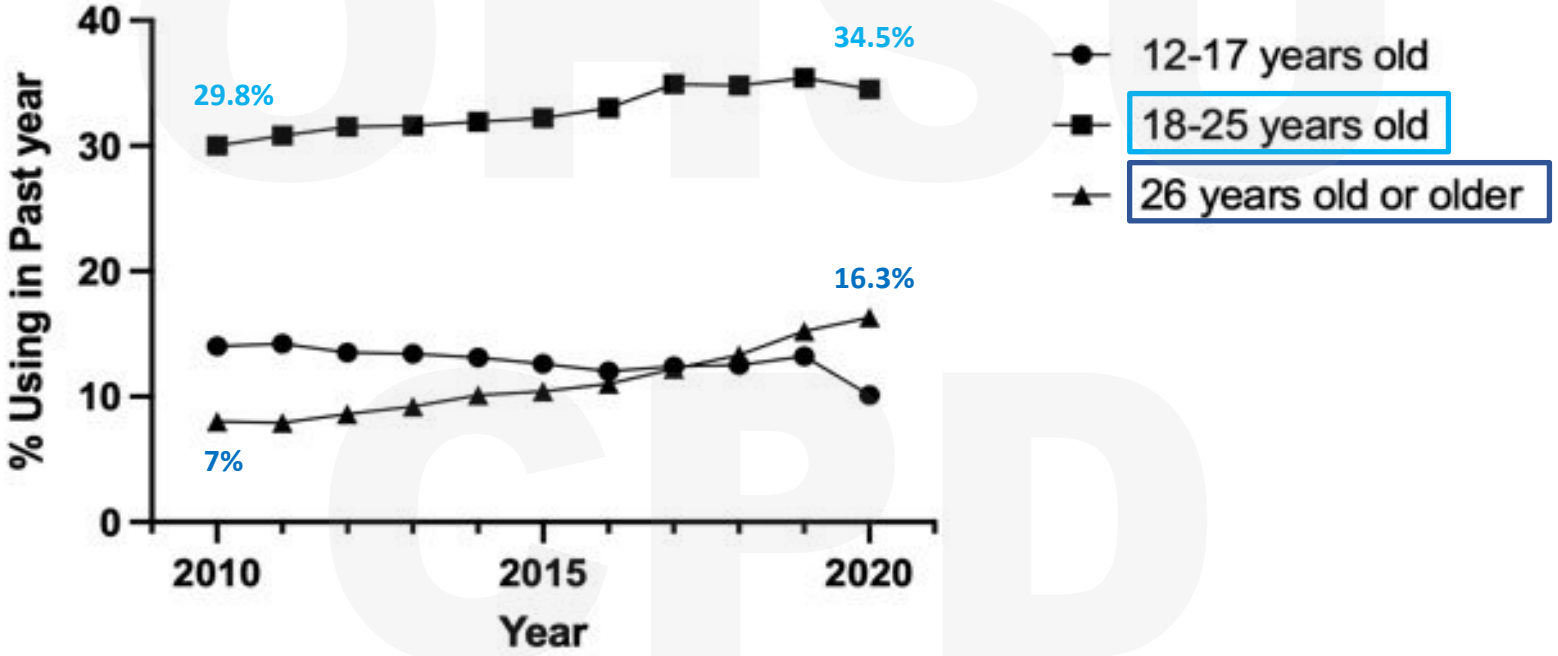
- 40 states and Washington DC have legalized medical cannabis
- 24 states and Washington DC have also legalized recreational (adult use) cannabis

Legal for recreational use | Legal for medical use | No comprehensive medical program | Decriminalized

Cannabis availability

Reference: Oregon Liquor Control Commission, Colorado Department of Revenue, Washington Liquor and Cannabis Board, Alaska Alcohol and Marijuana control office. 2019 Marijuana Business Daily.

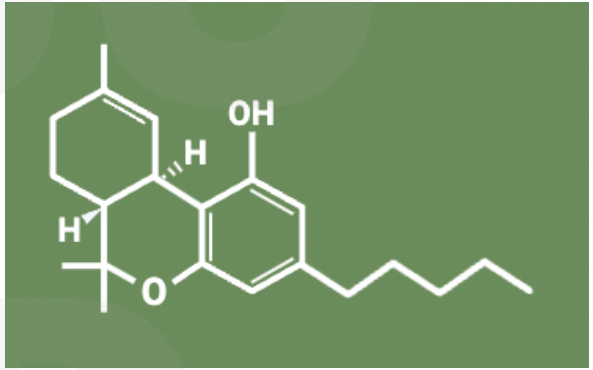
Prevalence of Cannabis Use



Reference: The National Survey on Drug Use and Health 2020 and 2022, Mehra 2023

Cannabis – more than just a weed

- ***Cannabis sativa* plant**
- Contains over 600 chemicals
- **Delta-9-tetrahydrocannabinol (THC)**
  - Main psychoactive component
  - Small and highly lipophilic
  - Rapidly distributed to the brain and fat
  - Metabolized by the liver
  - Half-life is 20-36hrs to 4-6 days
  - Can be detectable up to ~30 days

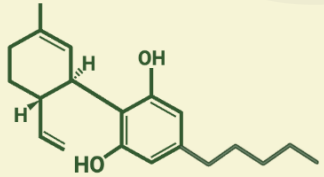


- **THC mechanism of action**: Partial binding at C1 (high affinity) and CB2
- **CBD mechanism of action**: more unknown

Synthetic: Delta-8 & Delta-10 THC

CBD
Cannabidiol

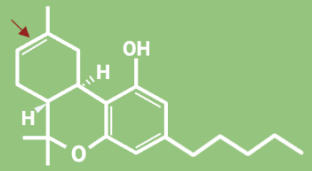
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 g/mol



Date Isolated: 1940
Is it psychoactive: No
Average Dose: 20-40 mg
Concentration in Cannabis: Up to 20%
Show up on a drug test?: No
Anecdotal experiences: Pain Relief+Relaxation

Delta-8 THC
Δ^8 Tetrahydrocannabinol

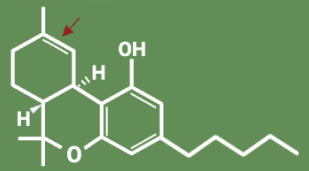
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 g/mol



Date Isolated: 1941
Is it psychoactive: Yes
Average Dose: 20-60 mg
Concentration in Cannabis: < 1%
Show up on a drug test?: Yes
Anecdotal experiences: Calming +Uplifting

Delta-9 THC
Δ^9 Tetrahydrocannabinol

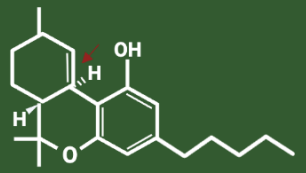
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 g/mol



Date Isolated: 1964
Is it psychoactive: Yes
Average Dose: 10-30 mg
Concentration in Cannabis: Up to 30%
Show up on a drug test?: Yes
Anecdotal experiences: Euphoric + Chill

Delta-10 THC
Δ^{10} Tetrahydrocannabinol

Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 g/mol



Date Isolated: 1984
Is it psychoactive: Yes
Average Dose: 20-60 mg
Concentration in Cannabis: < 1%
Show up on a drug test?: Yes
Anecdotal experiences: Energizing + creativity

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Limitations of the Urine Drug Screen

- Are often immunoassays that detect the major urinary metabolite of THC (11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid)

- Prone to false positives
  - NSAIDs and PPIs have been reported to cause false positives on drug screens
  - If a false positive or negative is suspected, confirmatory testing is with gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry

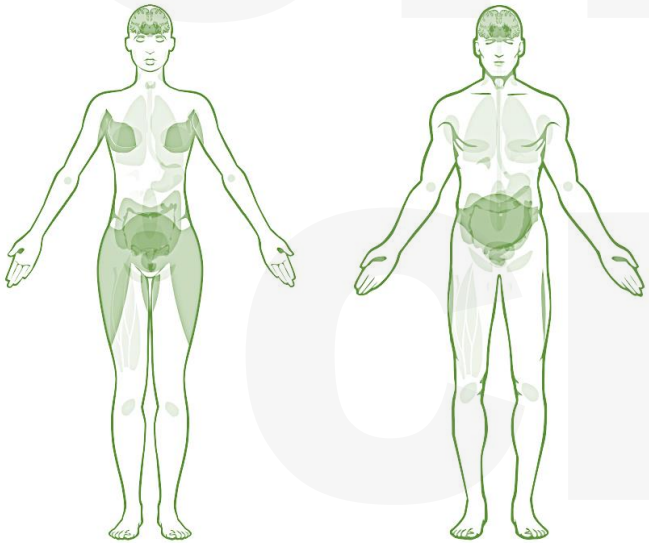
- Synthetic or designer cannabinoids are not detected by urine drug screens

Reference: Chocron et al. BMJ 2019; Wu et al. BMJ 2019

Cannabinoid Receptor Expression

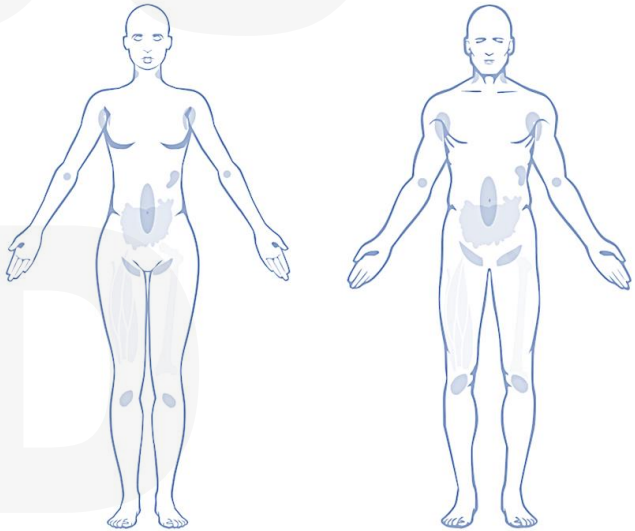
CB1

- Wide distribution of expression
- Enhanced expression in CNS, PNS and endocrine tissues
- Placenta
- Airway epithelial cells and endothelial cells



CB2

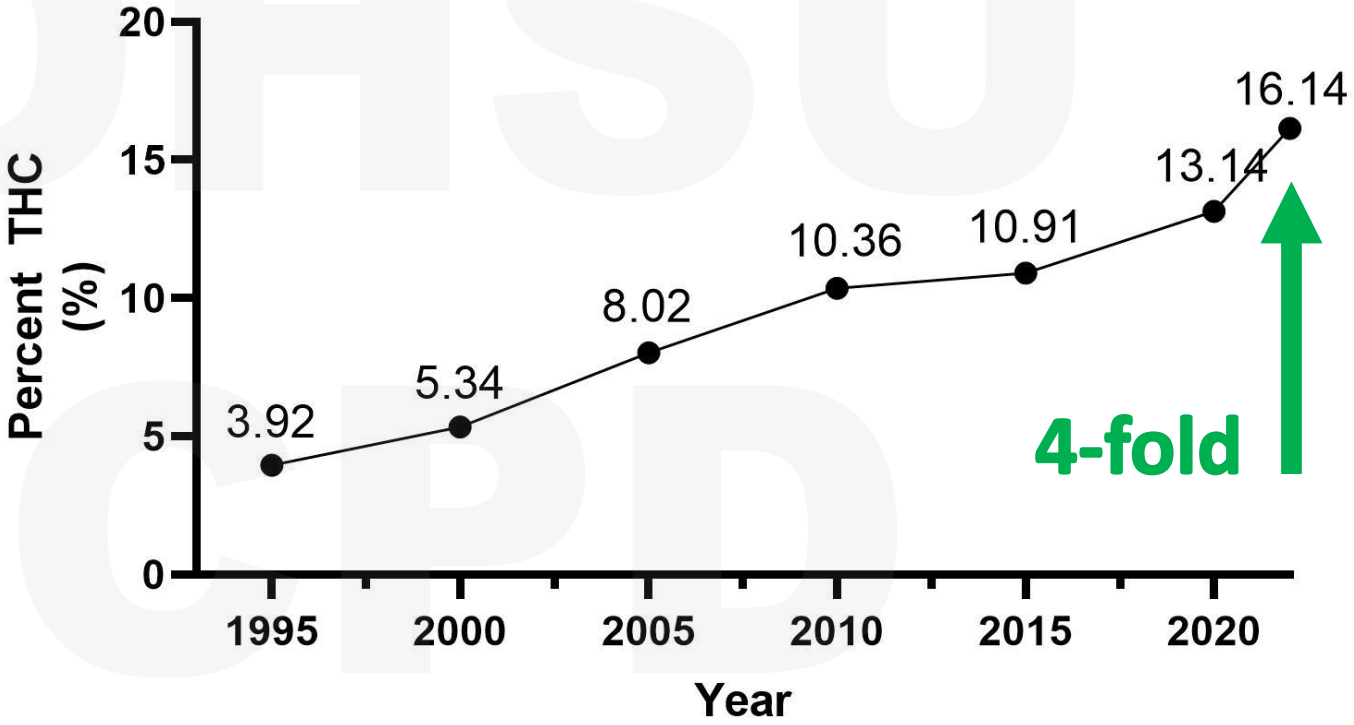
- Enhanced expression in immune-derived cells
- Expressed in airway macrophages, eosinophils, mast cells, most WBC



References: Human Protein Atlas (https://www.proteinatlas.org/ENSG00000118432-CNR1/tissue)

Increasing potency of cannabis

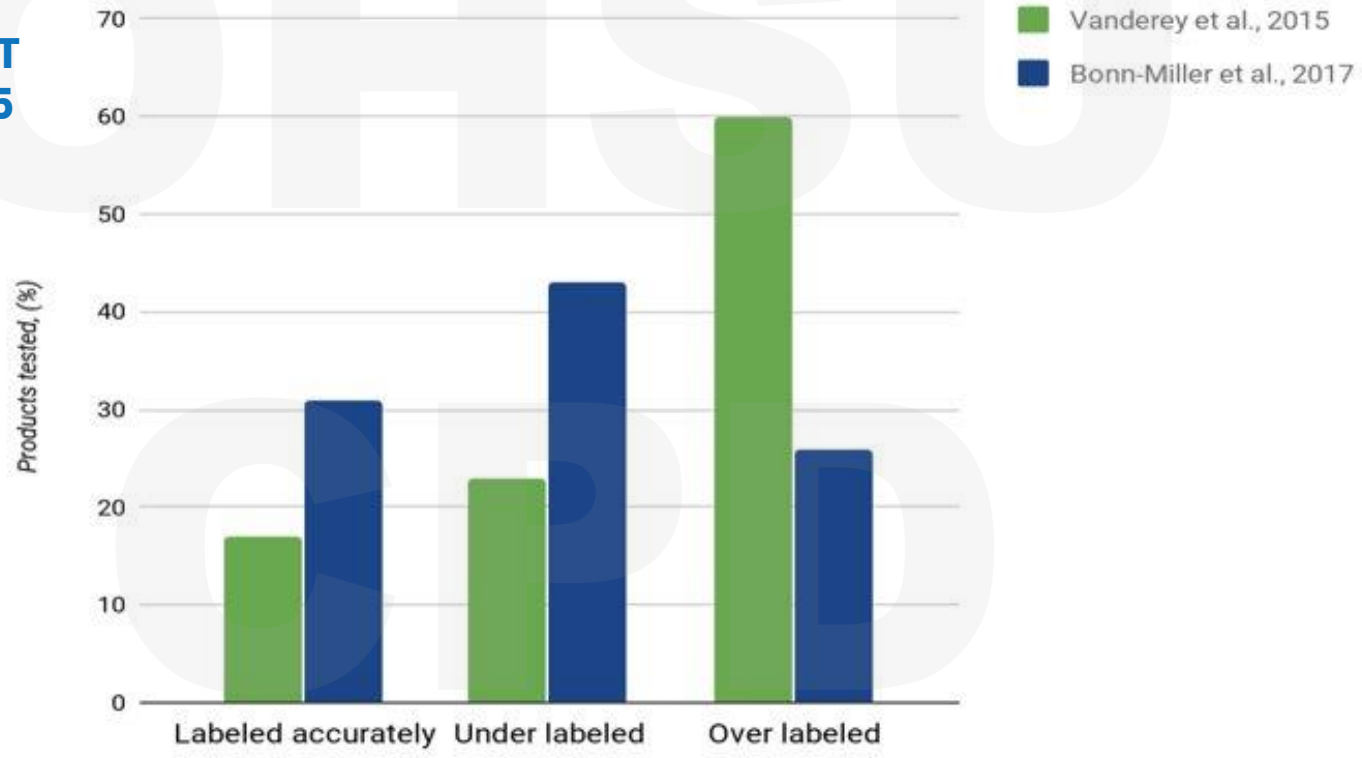
Percentage of THC in cannabis samples seized by the DEA (1995-2022)



Reference: Potency Monitoring Program, Quarterly Report #146, drugabuse.gov

Accuracy of Labeling

THC PRESENT IN 1 OUT OF 5 CBD-ONLY PRODUCTS



References: Vanderey et al. 2015, Bonn-Miller et al. 2017

Limitations of existing studies

- Recruitment bias
- Retrospective or observational design
- Patient self-report
- Confounded by tobacco, polysubstance use, small sample size, inaccurate dosing information
- Lack of quantification/timing of exposure
- Most studies reflect cannabis exposure through smoking
- Existing literature is largely from the 1980s when cannabis products were less potent

How Much THC are They Getting?

- Colorado Guidelines
  - 5 mg
  - 10 mg
  - 20-30 mg
- Harder to quantify
  - Dabbing (vaporized hash oil)
  - Smoking
  - Vaporizing
- So just ask

Reference: https://merryjane.com/news/legal-weed-convinced-over-150000-people-to-move-to-colorado-study-reports/

Cannabis and male reproductive health

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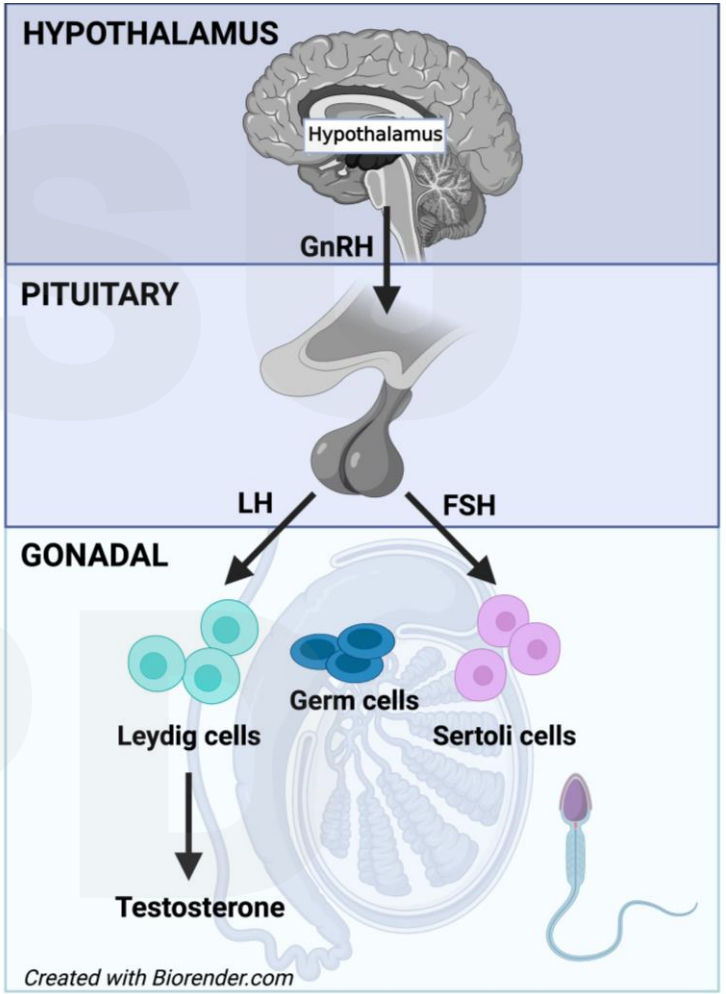
Male Hypothalamus-Pituitary-Gonadal (HPG) Axis



Reference: Wenger et al. 1999; created with biorender

Male Infertility Workup

- Semen Analysis (x2)
- Hormones:
  - Follicle stimulating hormone
  - Luteinizing hormone
  - Testosterone
- Testicular Volume
- Sexual Function

Semen Parameter	WHO 2021
Semen volume (mL)	1.4 (1.3–1.5)
Total sperm number (10^6 per ejaculate)	39 (35–40)
Total motility (%)	42 (40–43)
Progressive motility (%)	30 (29–31)
Non progressive motility (%)	1 (1–1)
Immotile sperm (%)	20 (19–20)
Vitality (%)	54 (50–56)
Normal forms (%)	4 (3.9–4)

Reference: World Health Organization 2021

Worsened semen parameters

- Strongest evidence of an adverse impact of cannabis on male fertility
- Reduction in:
  - Sperm count
  - Concentration
  - Motility
  - Viability
- Abnormal morphology
- Inhibition of capacitation and fertilization

Reference: Gundersen 2015, Pacey 2014, Carroll 2020, Hehemann 2021

Variable affect on hormones

- **Follicle stimulating hormone (FSH)**
  - no change
- **Luteinizing hormone (LH)**
  - Lower
  - Less response to GnRH
- **Testosterone**
  - Variable
  - Effect may be acute and transient

drlamcoaching.com

Sexual Desire is Increased

- **Any use:** increased coital frequency
  - 8.8 vs 7.8 events/month, p<0.05
- **Daily use:** 2 or more partners in previous year
  - OR 2.08 for men, 2.58 for women
- **Survey in Dispensary**
  - Increased orgasmic function
  - Improved erectile function
  - Higher sexual satisfaction

References: Smith 2010, Sun 2017, https://www.self.com/gallery/how-cannabis-affects-sex

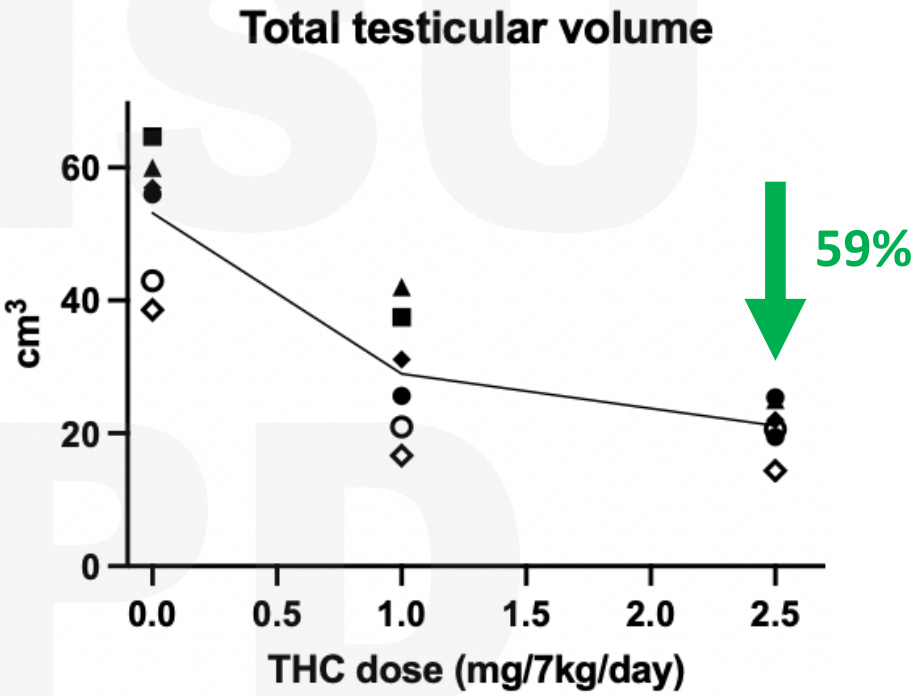
Erectile Function is Compromised

- Erectile dysfunction prevalence is doubled

- Orgasmic function
  - too quickly (OR 2.68)
  - too slowly (OR 2.05)
  - inability to reach (OR 3.94)

References: Elbendary 2009, Pizzol 2019

Testicular Volume is Decreased



References: Hedges et al. Fertil Steril 2022, https://www.cnn.com/2023/05/16/health/marijuana-harm-early-pregnancy-wellness/index.html

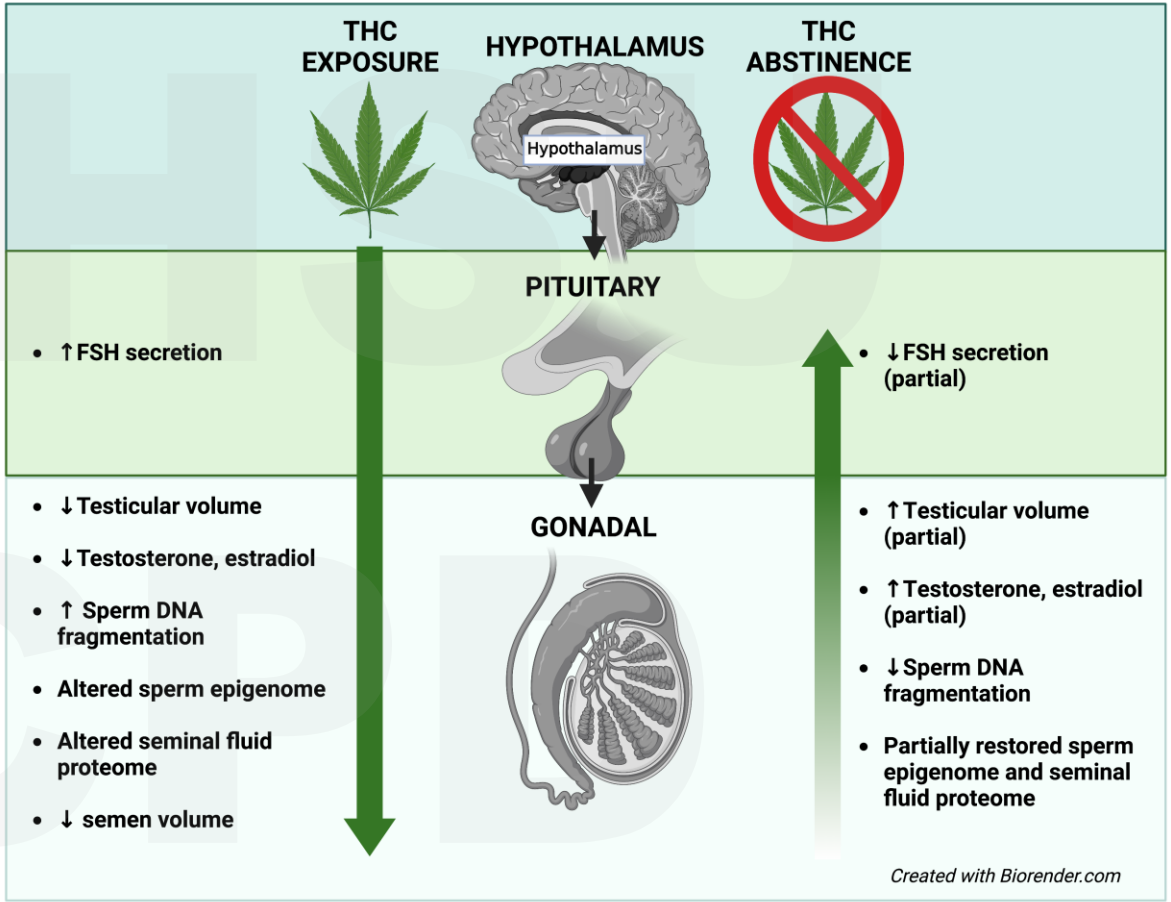
Spontaneous Abortion Increases

- 1,535 North American couples from 2013-2019
- Preconception cannabis use:
  - <1 time/week: 9%
  - ≧ 1 time/week: 8%
- Couples with male partners who used cannabis ≧ 1 time/week preconception had a higher risk of spontaneous abortion
  - HR 2.0 (CI 1.2-3.1)
  - Even with non-using female partner

References: Harlow 2021

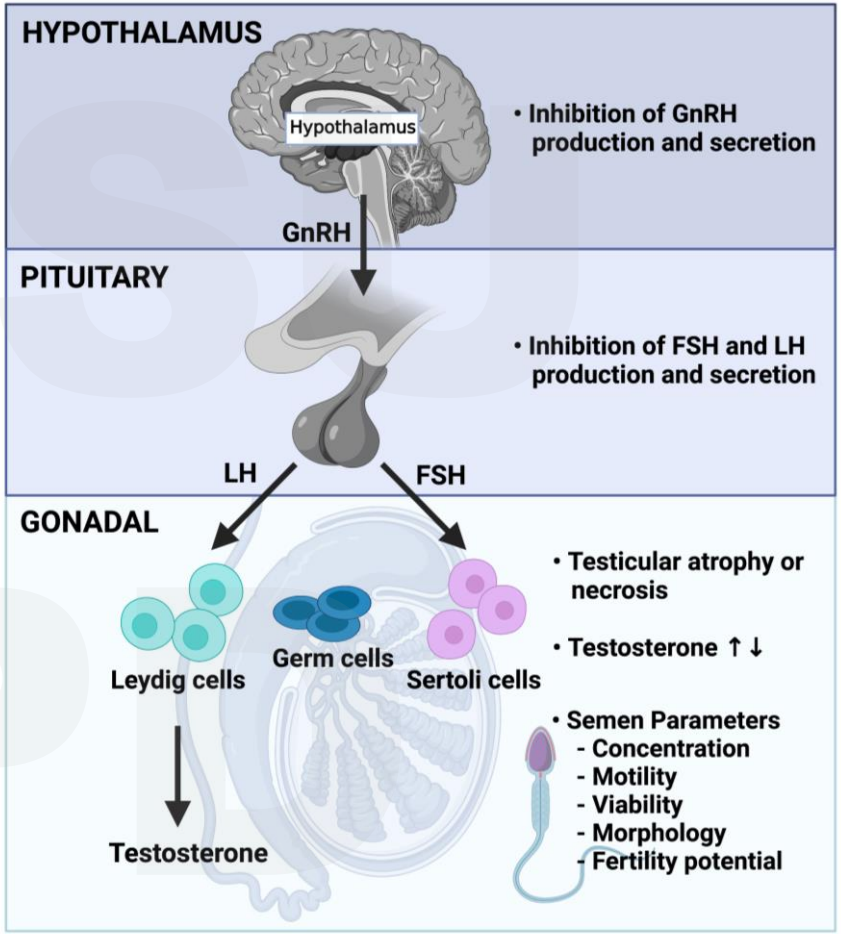
Possibility for recovery?

- Rhesus macaques (n=6) with THC exposure for ~7 months
- THC discontinued for 4 months
- Partial recovery noted



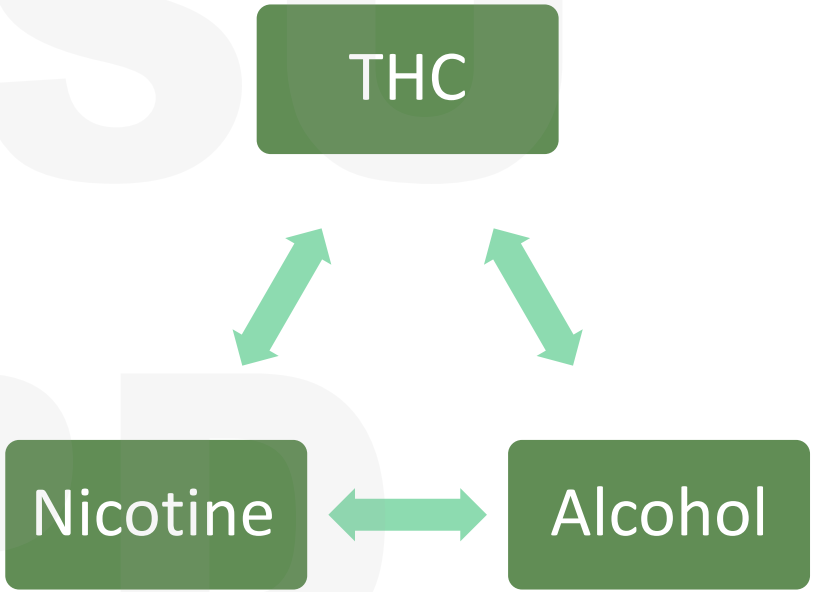
Take-Home Points

- Cannabis use is increasing among reproductive aged men
- Negative impact on fertility and sexual health, with likely dose-dependent and reversible effects
- Men interested in fertility should be counselled towards cessation or decreased use
- Those using cannabis medically should weigh the benefits of use with potential fertility risks and attempt reduced consumption



Impact of Cannabis Co-Use

- Nicotine:
  - Reduced sperm health
  - ED (Nitric oxide perturbation)
  - Low libido
  - Increased pregnancy loss (dose-dependent)
  - Birth defects (dose-dependent)
  - Abnormal offspring neurobehavior
  - Heritable decreased fertility



References: du Fossé 2021, Zhou 2020, Hawkey 2019, Sharma 2016, Kovac 2015, Gundersen 2015

Cannabis and female reproductive health

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Cannabis and Female Sexual Function

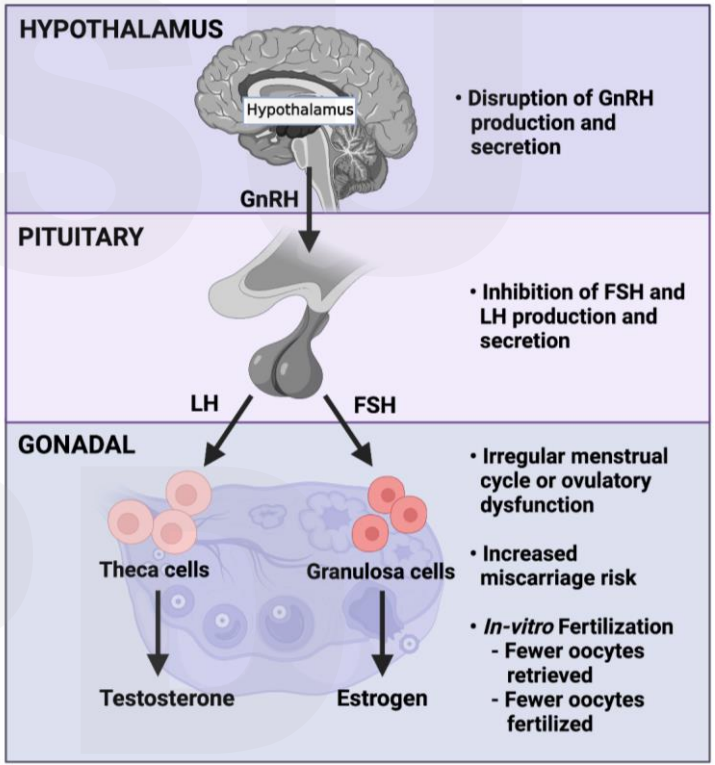
- Overall mixed research findings – challenges with objective measurements
- Potential adverse affects:
  - Variability in response (e.g., individual, dose, strain)
  - Dose-dependent (higher vs. lower doses may have inhibiting effects)
  - May inhibit orgasm
- Potential benefits include:
  - Increased orgasm frequency and satisfaction
  - Enhanced arousal, pleasure, and sensory focus
  - Reduced anxiety and inhibitions
  - Relief from urogenital pain

References: Mulvehill et al. Sexual Medicine 2024; Lynn et al. Sexual Medicine Reviews 2020; Kasman et al. Sexual Medicine 2020

Cannabis Use on Fertility

Prior human studies are limited by:

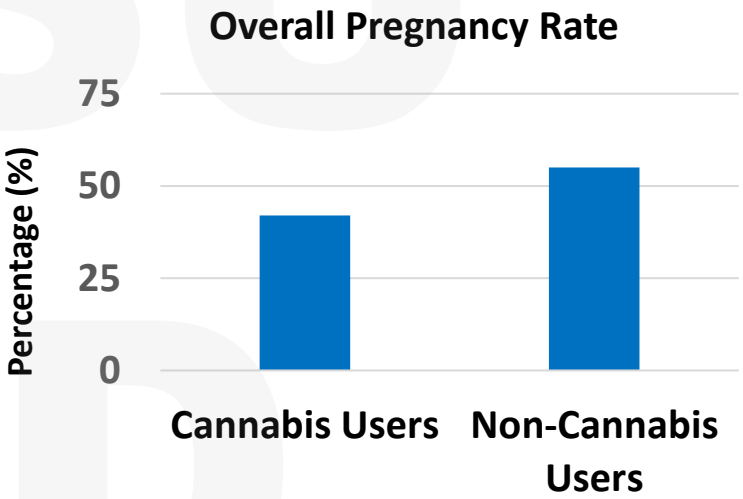
- Difficulty defining dose/exposure
- Polysubstance Use
- Non-physiologic route of ingestion



Reference: Nassan et al. 2019; Wise et al. 2018; Klonoff-Cohen et al. 2006; Asch et al. 1980

Cannabis use decreases probability to conceive

- Prospective cohort study (n=1,228) of women aged 18-40yo with prior pregnancy loss in 2006-2012
- Preconception use was associated with reduced fecundability (OR 0.59; 95% CI 0.38-0.92)
- Preconception use was associated with:
  - Increased frequency of intercourse per cycle
  - Anovulation
  - Decreased live births
- No association with pregnancy loss



References: Mumford et al. 2021

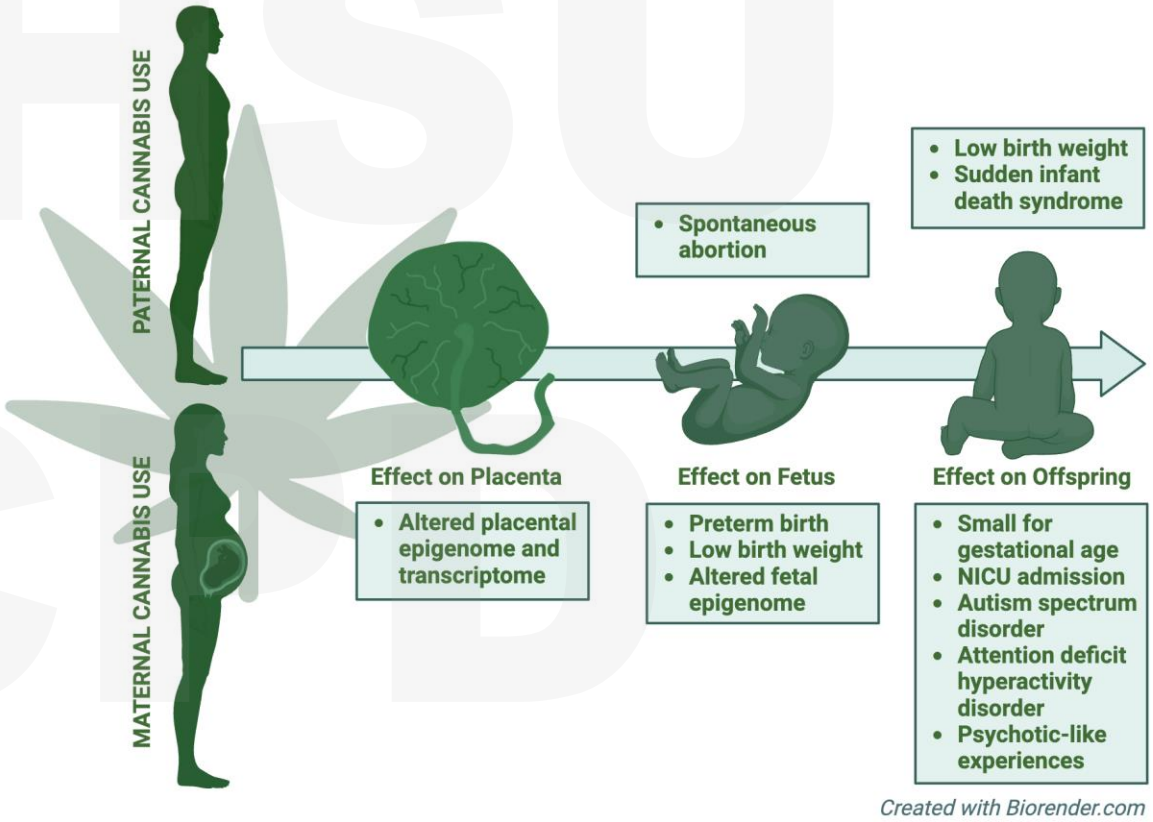
Take-Home Points

- For most couples, cannabis use likely will not affect their ability to conceive but for couples with subfertility or infertility, it could be a contributing factor
- Impact the body's natural hormone cycles
- Increase the risk for miscarriage
- Exacerbate existing infertility factors

https:Insider.com

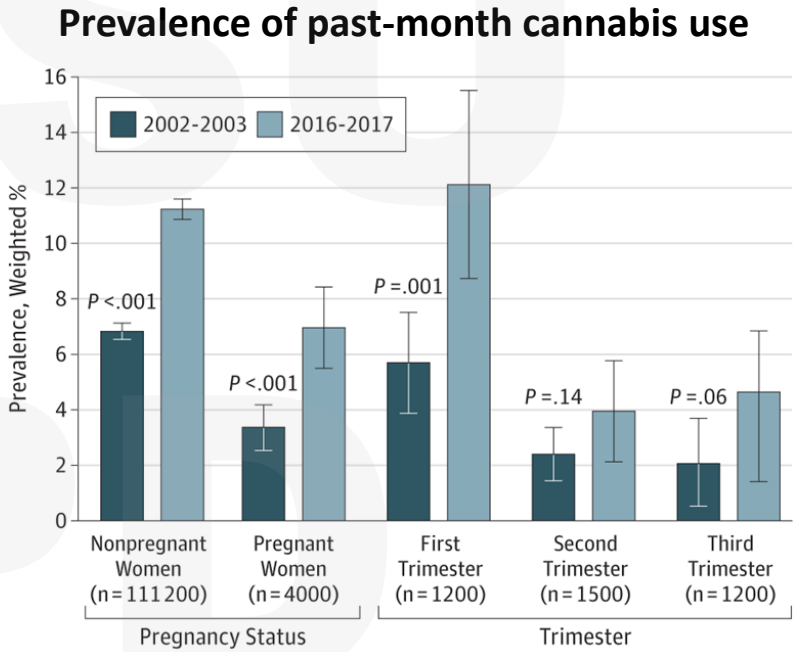
Preconception cannabis use and impact on offspring

- Paternal cannabis use
  - Impacted sperm DNA methylome that can persist despite cessation
  - Select sperm DNA methylation changes and genes affected are associated with developmental processes
  - May influence short- and longer-term offspring health
- Maternal cannabis use
  - Increased anxiety behavior and perturbation of the brain epigenome in offspring
  - Increased offspring addiction vulnerability later in life



Cannabis Use in Pregnancy

- Most commonly used federally illicit drug in pregnancy
- Self-reported use in pregnancy ranges from 2% to 30%
- Potency of cannabis products has increased 3-fold the last 20 years



References: Volkow et al. 2017; Jarlenski et al. 2017; Brown et al. 2017; Young-wolff et al. 2019; Young-Wolff et al JAMA 2017; Rodriguez et al. BJOG 2019, Young-wolff et al. JAMA 2021

Perceived Benefits

Survey respondents – WIC mothers	Ever use % (n)	Current use % (n)	Past use % (n)
To help with depression/anxiety/stress	35% (164)	63% (60)	28% (103)
To help with pain	29% (135)	60% (57)	21% (78)
To help with nausea/vomiting	23% (108)	48% (46)	17% (62)
For fun/recreation	59% (277)	39% (37)	65% (240)
Other reason	16% (75)	14% (13)	16% (58)

References: Albanese et al. Monitoring Health Concerns Related to Marijuana in Colorado, 2014

Where Do Patients Get Their Information?

- **Limited health care counseling**
- **Internet searches**
- **Parenting blogs, online groups**
- **Dispensaries**

Where Do Our Patients Get Information?

- Statewide cross-sectional study of dispensaries in Colorado (n=400)
- Mystery shopper study, caller was 8 weeks pregnant with nausea
- Nearly 70% had a product recommendation, predominantly edibles
- 65% based recommendations on personal opinion
- 32% recommended discussing with OB provider without prompting

Phone Script Cited Here...

"Hi, I'm 8 weeks pregnant and feeling really nauseated. Are there any products that are recommended for morning sickness?"

Prompts in response to no recommendation:

- 1. What if I have a medical card? (If asked why you have a card, state it is for chronic pain from a car accident.)
- 2. Why not?

Prompts in response to recommendation:

- 1. What product?
- a. Why?
- 2. How often should I use it?
- 3. Is it safe to take during pregnancy?
- a. If only maternal risks are addressed, ask: Is it also safe for my baby?
- b. If only fetal risks are addressed, ask: Is it also safe for me?

Before closing call:

Should I talk to my doctor about this (if no recommendation previously made to discuss with health care provider)?

References: Dickson 2018 et al.

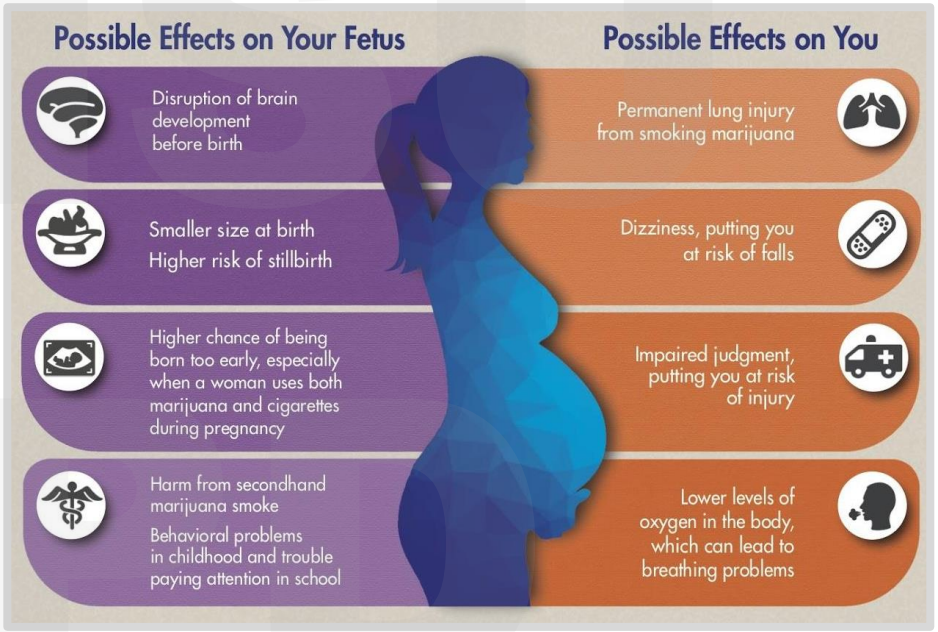
Outcomes of Prenatal Cannabis Exposure

Maternal

- Increased risk of anemia
- Increased cyclic vomiting and/or hyperemesis syndrome
- Increased hypertensive disorders

Fetal/Neonatal

- Fetal growth restriction and lower birth weight
- Preterm birth
- Stillbirth and miscarriage
- Increased NICU admissions
- Altered neurodevelopment



References: ACOG; Hayer et al., 2023; Lo et al., 2023; Marchand et al. 2022; Conner et al. 2016; Young-Wolff et al. 2024

Impact of Prenatal Cannabis Use on Offspring

Prenatal cannabis exposure is associated with an increased risk of:

Infancy

- Decreased ability to self-soothe
- Sleep disturbances

Childhood

- Poorer memory, verbal reasoning skills
- Less attentive, more impulsive and hyperactive
- Symptoms of depression, anxiety

Adolescence

- Continued hyperactivity, impulsivity, inattention
- Reduced school performance

References: Thompson et al. Obstetl & Gynecol Survey 2019; https://resources.beststart.org/wp-content/uploads/2019/01/A30-E.pdf, Huizink et al. 2014, Day et al 1994., Fried et al. 1995

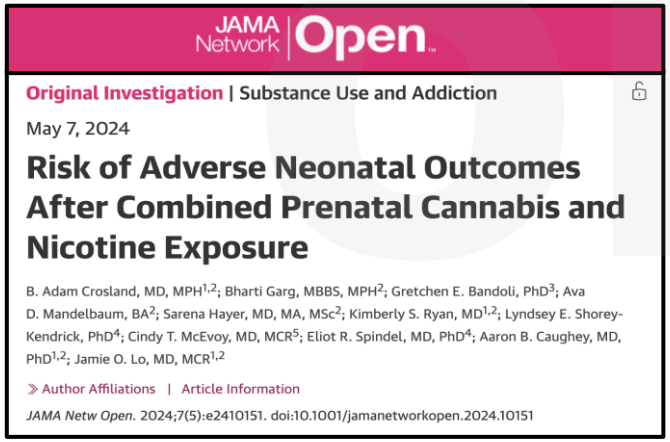
Cannabis and Nicotine-product Co-Use

Co-use of nicotine and cannabis vs. none is associated with a 4-fold increased risk in infant death, and nearly a 2-fold increased risk vs. use of nicotine or cannabis alone

Outcome	Substance used, % of participants			
	Unexposed (n = 3 039 129)	Cannabis-use (n = 23 007)	Nicotine-product use (n = 56 811)	Both (n = 10 312)
Hypertensive disease[b]	7.6	12.3	9.6	11.2
Preterm delivery <37 wk	6.6	12.2	12.0	17.5
Preterm delivery <32 wk	0.8	2.1	1.8	2.9
SMM	1.3	2.3	2.1	2.6
Nontransfusion SMM	0.4	0.8	0.7	1.0
NICU admission	10.0	15.6	17.8	22.5
Small for gestational age	8.5	14.3	13.7	18.0
Respiratory distress syndrome	3.4	5.9	5.5	7.5
Infant death	0.3	0.7	0.7	1.2
Neonatal death	0.2	0.3	0.3	0.6
Postneonatal death	0.1	0.4	0.4	0.6
Hypoglycemia	2.1	3.5	3.0	3.8
Bronchopulmonary dysplasia	0.1	0.2	0.1	0.2

Reference: Crosland et al. JAMA Network Open 2024

Cannabis and Nicotine-product Co-Use



JAMA Network Open

Original Investigation | Substance Use and Addiction

May 7, 2024

Risk of Adverse Neonatal Outcomes After Combined Prenatal Cannabis and Nicotine Exposure

B. Adam Crosland, MD, MPH[1,2]; Bharti Garg, MBBS, MPH[2]; Gretchen E. Bandoli, PhD[3]; Ava D. Mandelbaum, BA[2]; Sarena Hayer, MD, MA, MSc[2]; Kimberly S. Ryan, MD[1,2]; Lyndsey E. Shorey-Kendrick, PhD[4]; Cindy T. McEvoy, MD, MCR[5]; Eliot R. Spindel, MD, PhD[4]; Aaron B. Caughey, MD, PhD[1,2]; Jamie O. Lo, MD, MCR[1,2]

Author Affiliations | Article Information

JAMA Netw Open. 2024;7(5):e2410151. doi:10.1001/jamanetworkopen.2024.10151

Co-use of nicotine and cannabis vs. none is associated with a **4-fold** increased risk in infant death, and nearly a **2-fold** increased risk vs. use of nicotine or cannabis alone.

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Bronchopulmonary dysplasia	0.1	0.2	0.1	0.2

Reference: Crosland…Lo, J. JAMA Network Open 2024

Offspring Vulnerability to Drug Addiction

- The endocannabinoid system regulates dynamic changes to reward pathways:
  - Mesolimbic dopamine pathway
  - Reward-associated behaviors

- Cannabis exposure in the prenatal and postnatal period can potentially disrupt normal development and increase vulnerability to drug addiction

- More notable in male offspring

- Dose-dependent effect

References: Hurd et al. J Neurosci 2019; Hurd et al. Neurotoxicol Teratol 2005; Spano et al. Biol Psychiatry 2007; Tortoriello et al. EMBO 2014

Transfer of Cannabis in Breastmilk

- 84% of women who used while pregnant continued while breastfeeding
- About 2.5% of inhaled cannabis is transferred into breastmilk
- 56% of new parents did not know THC is transferred to breast milk
- Only 30% of patients report receiving postnatal counseling on THC in breast milk
- Exposed infants scored poorly on Psychomotor Developmental Index

References: Baker et al., 2018; Astley et al. 1990, Bertrand et al. 2018

Cannabis and Menopause – US study

- Perimenopausal (n=131) and post-menopausal (n=127) participants completing surveys on symptomatology and cannabis use
- 86.1% reported current cannabis use with 78.7% for menopause-related symptoms
  - Most common is for sleep disturbance (67.4%) and mood/anxiety (46.1%)
- Perimenopausal participants had an increased use of cannabis to treat menopause-related mood/anxiety symptoms compared to postmenopausal participants
- Modes of cannabis use:
  - Smoking (84.3%)
  - Edibles (78.3%)

References: Dahlgren et al. 2022. Menopause

Cannabis and Menopause – Canada study

- 1,485 participants surveyed – median age 49yo
    - Perimenopausal (33%), postmenopausal (35%)
- 499 (34%) reported current cannabis use and 978 (66%) indicated ever using cannabis
- Most common reasons for cannabis use were sleep (65%), anxiety (45%) and muscle/joint achiness (33%)
- 74% of current users reported it was helpful for symptoms

References: Babyn et al. 2023. BMJ Open

Harm Reduction Approaches

"**Harm reduction** is the idea that since we cannot completely eliminate risk and harm, we should do our best to minimize them."

National Harm Reduction Coalition & Academy of Perinatal Harm Reduction

- Consider substituting form of cannabis used
- Avoid synthetic cannabis or cannabis concentrates
- If inhalation, use a vaporizer to avoid risk of exposure to pyrolytic compounds
- Do not mix cannabis with tobacco
- Do not use a cigarette filter when using

References: Lucas et al., 2018; Winstock et al. 2010; Lau et al. 2015

Provider Resources

- SAMHSA – Substance Use and Mental Health Services Administration
- STEM (Systematically Testing the Evidence on Marijuana www.cannabisevidence.org
- Colorado Cannabis – www.cannabis.Colorado.gov
- Canada Cannabis - www.canada.ca/en/services/health/campaigns/cannabis/health-effects.html
- American Society of Reproductive Medicine - https://www.asrm.org/topics/topics-index/alcohol-and-drug-use/

Thank You

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