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

56th Annual Primary Care Review

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DATE: February 10th, 2024

Disclosures

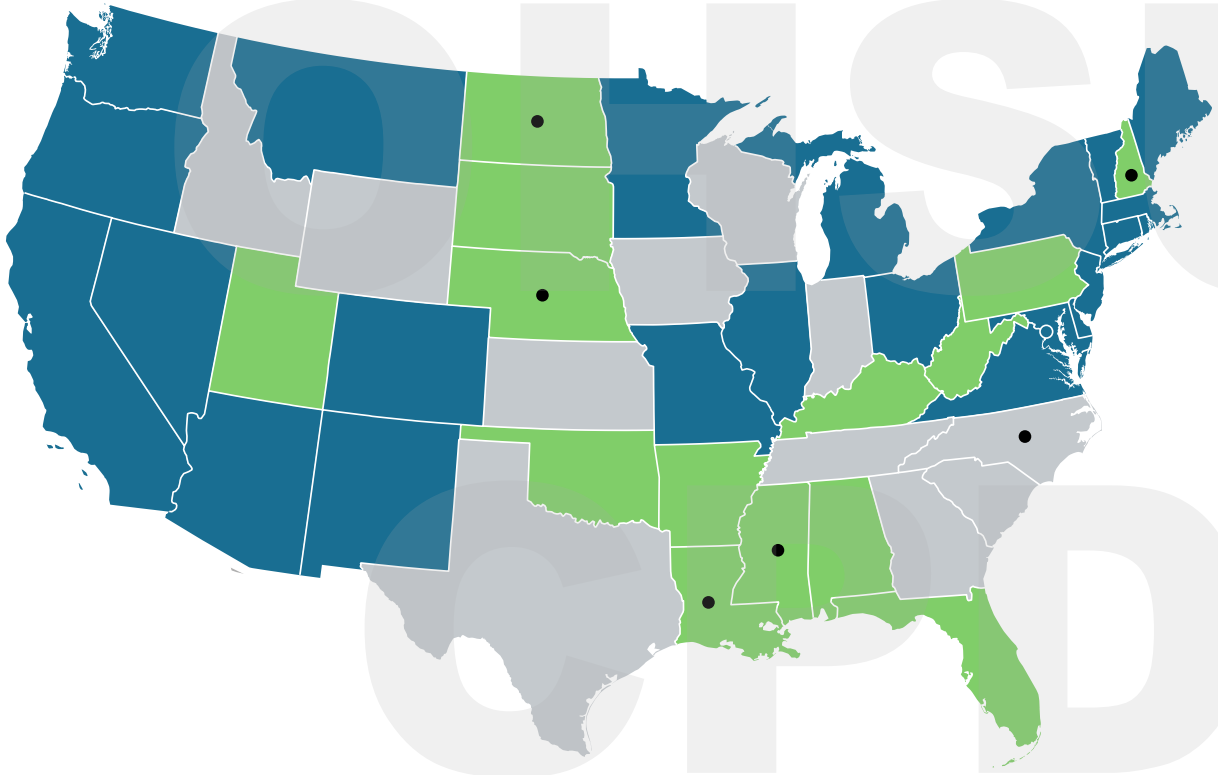
No financial disclosures

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



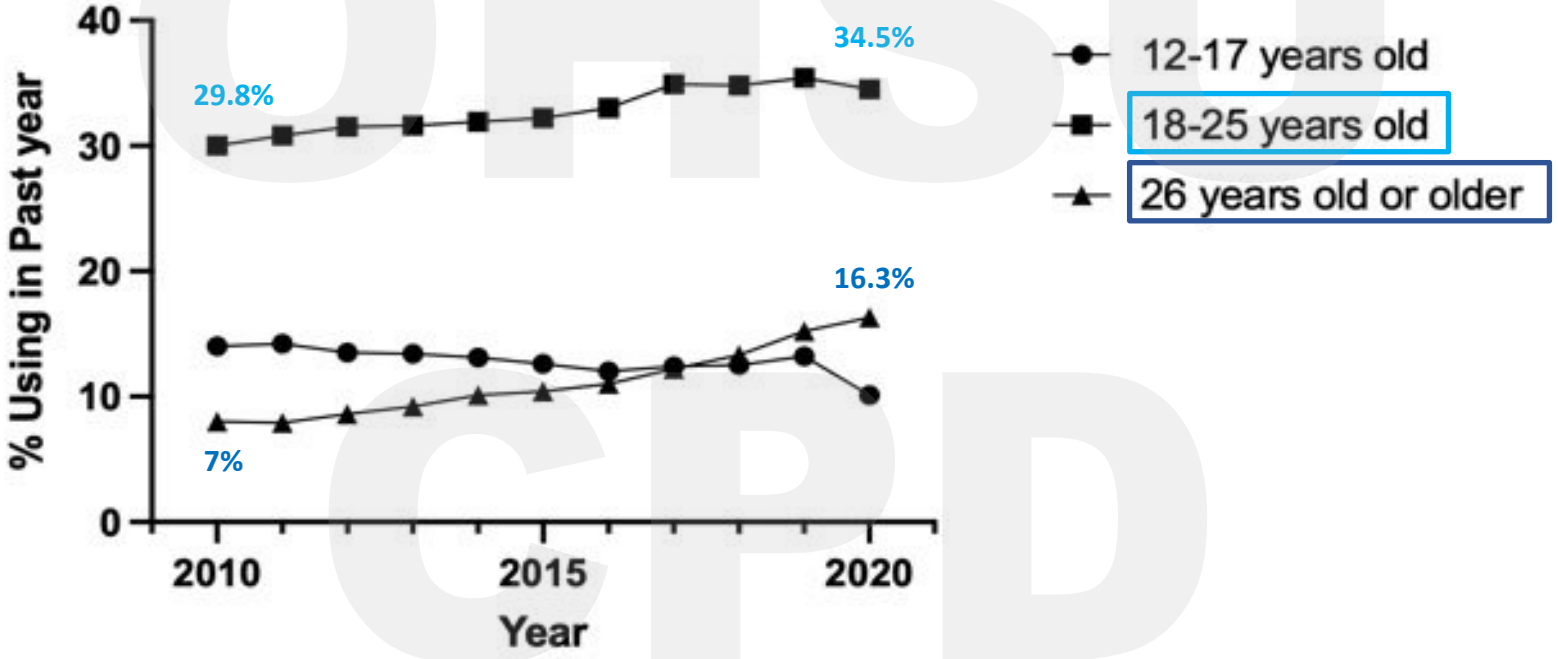
- 40 states and Washington DC have legalized medical cannabis
- 24 states and Washington DC have also legalized recreational (adult use) cannabis

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

Cannabis availability

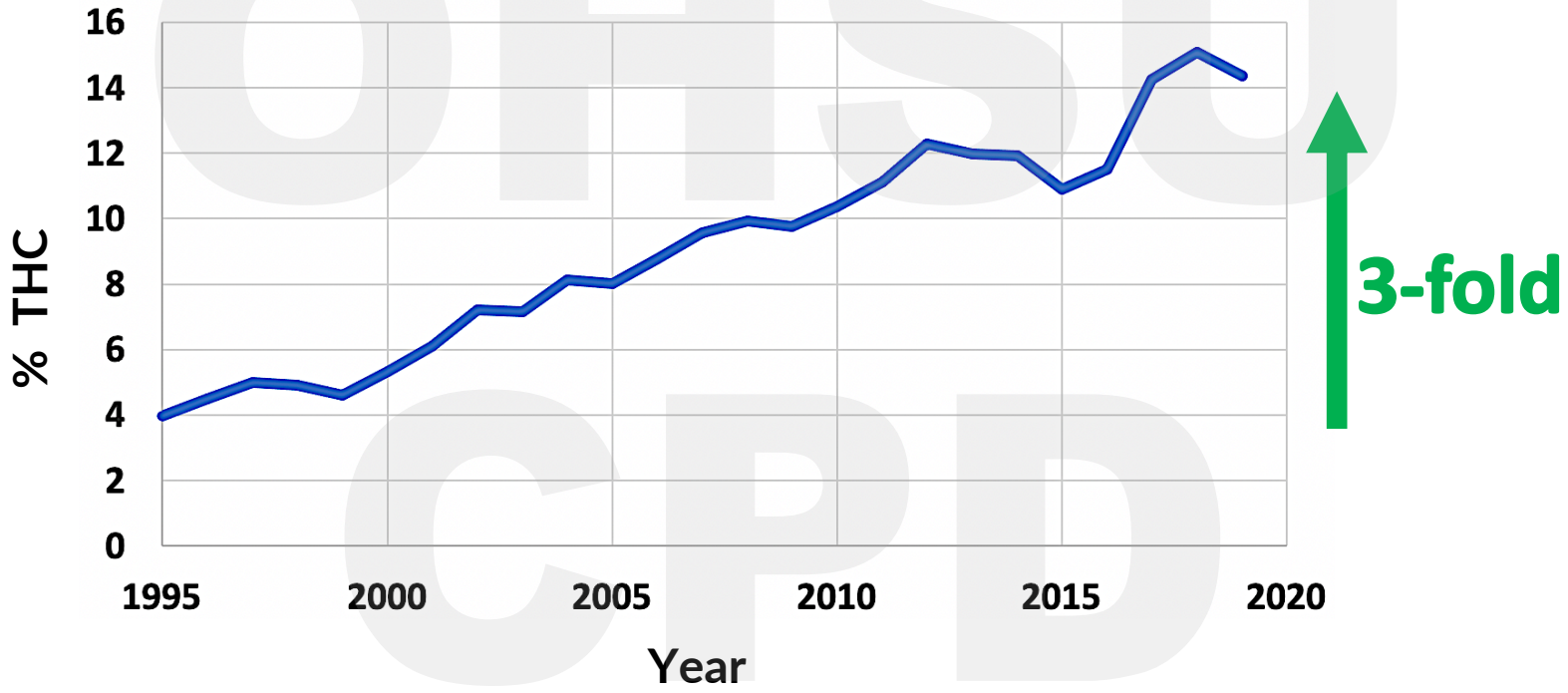
Reference: Oregon Liquor Control Commission, Colorado Department of Revenue, Washington Liquor and Cannabis Board, Alaska Alcohol and Marijuana control office. 2019 Marijuana Business Daily.

Prevalence of Cannabis Use



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

Increasing potency of cannabis



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

Cannabis - More than just a weed

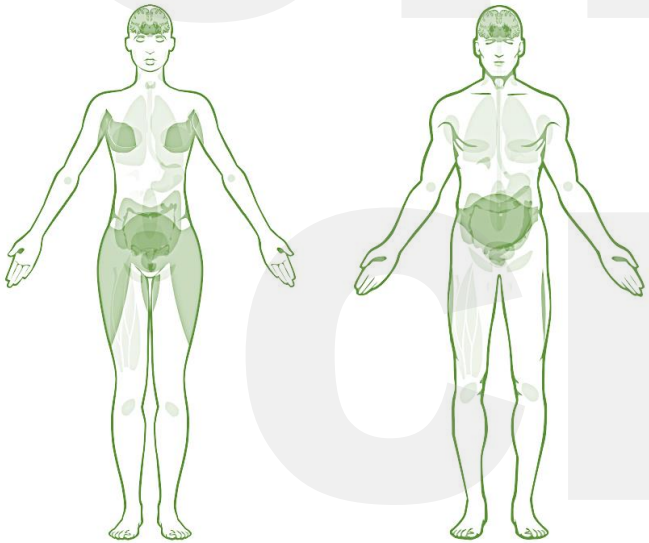
- ***Cannabis sativa* or *indica* plant**
- Contains over 600 chemicals
- **Delta-9-tetrahydrocannabinol (THC):**
  - Main psychoactive component
  - Small and highly lipophilic
  - Rapidly distributed to the brain and fat
  - Metabolized by the liver
  - Half-life is 20-36hrs to 4-6 days
  - Can be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

References: Rossato 2005, Sohly 2014, Huestis 2007

Cannabinoid Receptor Expression

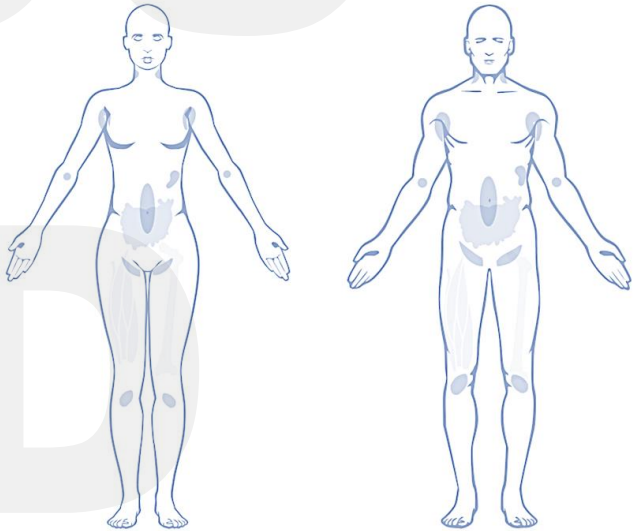
CB1

- 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



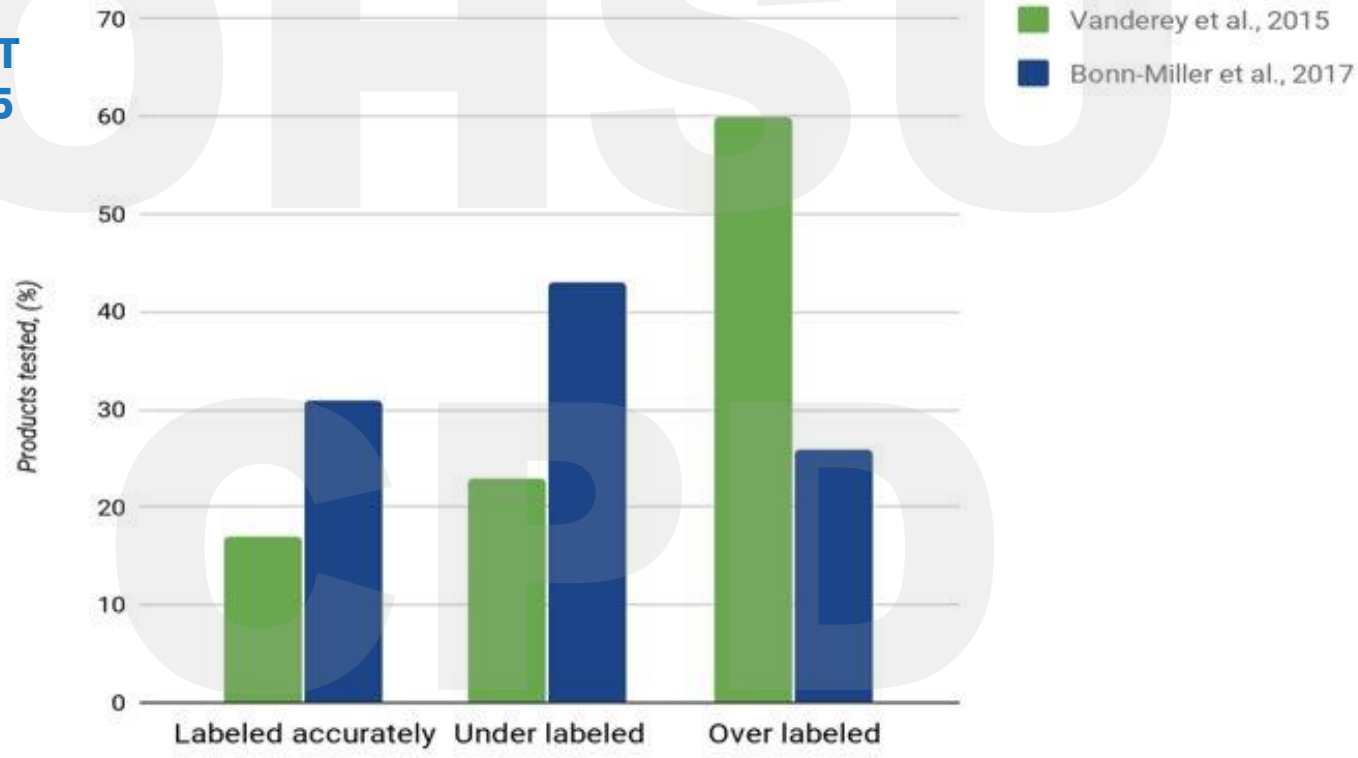
References: Human Protein Atlas (https://www.proteinatlas.org/ENSG00000118432-CNR1/tissue)

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

Accuracy of Labeling

THC PRESENT IN 1 OUT OF 5 CBD-ONLY PRODUCTS

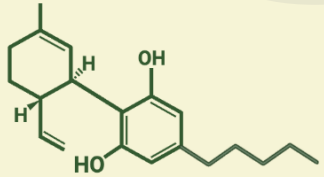


References: Vanderey et al. 2015, Bonn-Miller et al. 2017

Synthetic: Delta-8 & Delta-10 THC

CBD
Cannabidiol

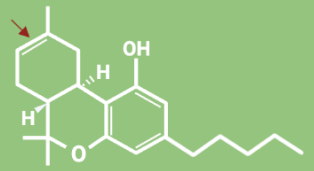
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 g/mol



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

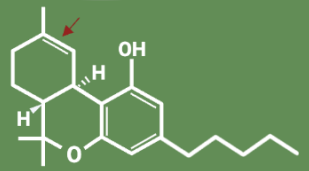
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 g/mol



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

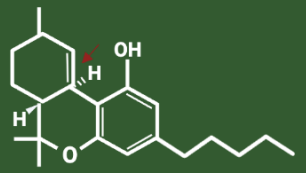
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 g/mol



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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Cannabis and male reproductive health

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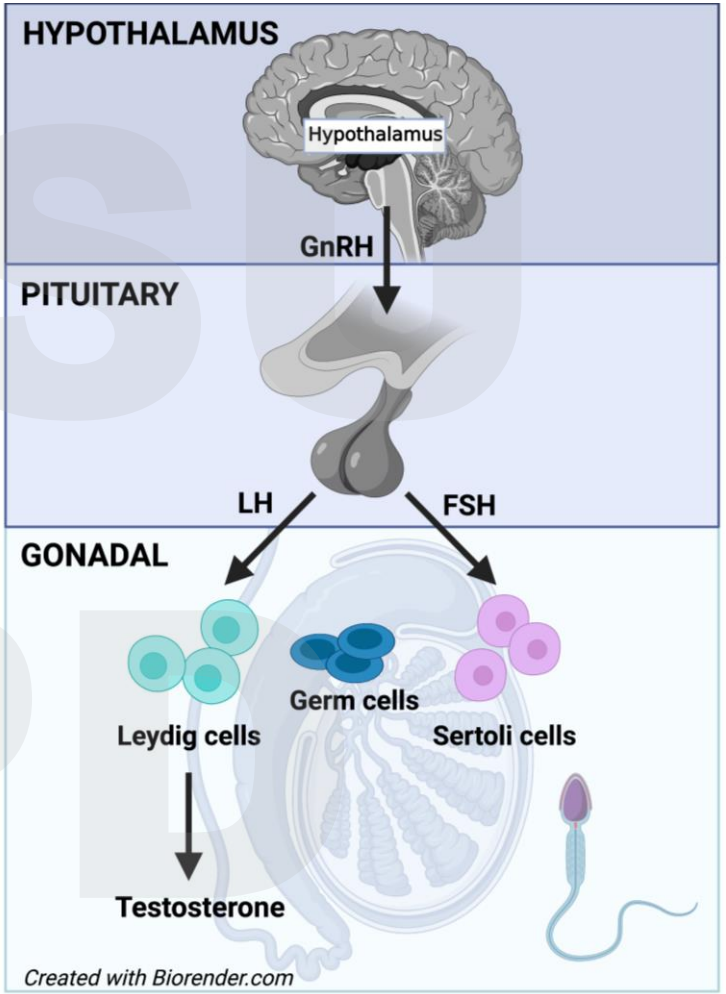
Male Hypothalamus-Pituitary-Gonadal (HPG) Axis



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

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Chronic delta-9-tetrahydrocannabinol exposure impacts testicular volume and male reproductive health in rhesus macaques

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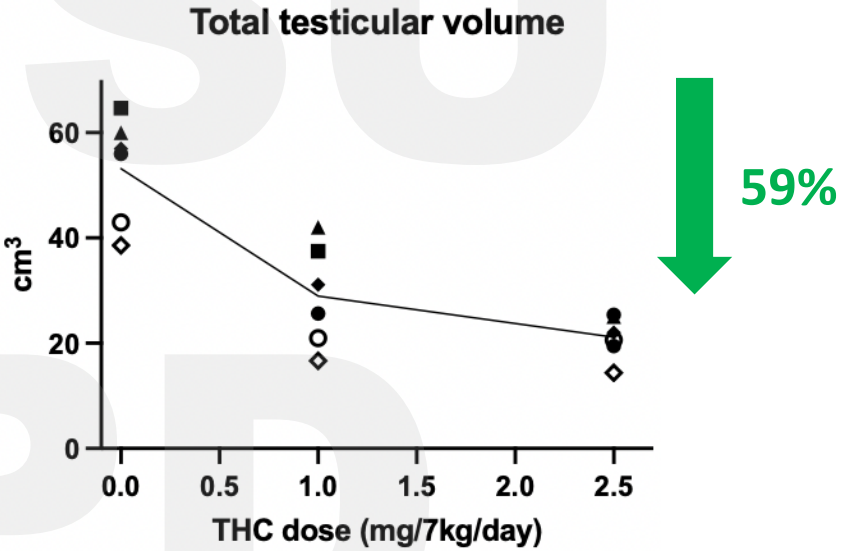


References: Hedges et al. Fertil Steril 2022

Gundersen – The Danish Study (2015)

- 1,215 men (18-28 yo) undergoing military service screening from 2008-2012
- Cannabis use categories: 1) none, 2) once per week or less, 3) more than once a week
- 45% smoked cannabis within the prior 3 months
- Cannabis more than once per week
  - 28% lower sperm concentration (95% CI: −48, −1)
  - 29% lower total sperm count (95% CI: −46, −1)
- Cannabis more than once per week and other recreational drugs
  - 52% lower sperm concentration (95% CI: −68, −27)
  - 55% lower total sperm count (95% CI: −71, −31)

Gundersen – The Danish Study

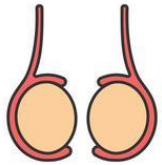
- Cannabis smokers had higher levels of testosterone
  - Similar to cigarette smokers

- Men who had used cannabis during the last 3 months had higher:
  - Alcohol and caffeine intake
  - Prevalence of smoking tobacco
  - Intrauterine tobacco exposure
  - Stress and sleep score
  - Prevalence of sexually transmitted diseases
  - Use of recreational drugs

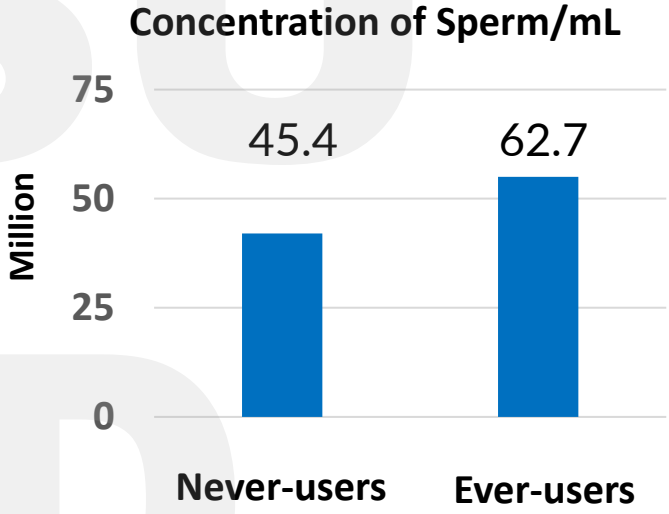
Thistle – The NHANES Study (2017)

- US National Health and Nutrition Examination Survey (NHANES)
- 1,577 men from 2011-2012
- Cannabis use:
  - Ever-users: 66.2%
  - Current users: 26.6%
- Testosterone
  - No difference between ever-users and never-users
  - Inversely associated with time since last regular use (p-value for trend = 0.02)
    - Trend stronger in younger men (age 18-29, $p<0.01$)
  - Recency of use stronger than duration or frequency

Nassan – The Markers Study (2019)

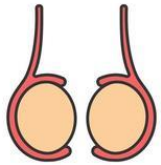


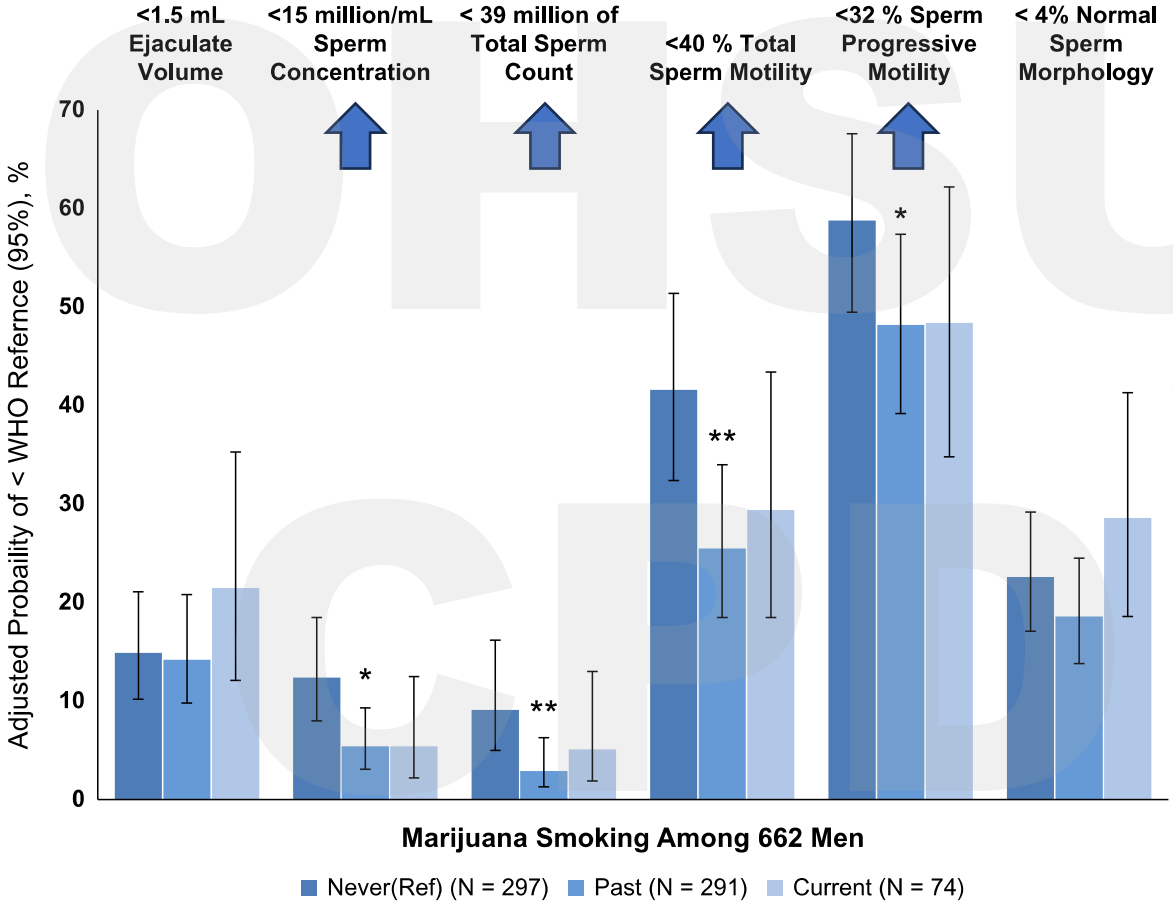
- 662 subfertile men at MGH Fertility Center (2000-2017)
- Semen and blood samples were obtained and analyzed
- FSH is 16% lower in THC smokers
- No difference in sperm DNA fragmentation, LH, testosterone, or estradiol
- **Sperm concentration**
  - Current vs prior smoker: no difference



(p = 0.0003)

Nassan – The Markers Study





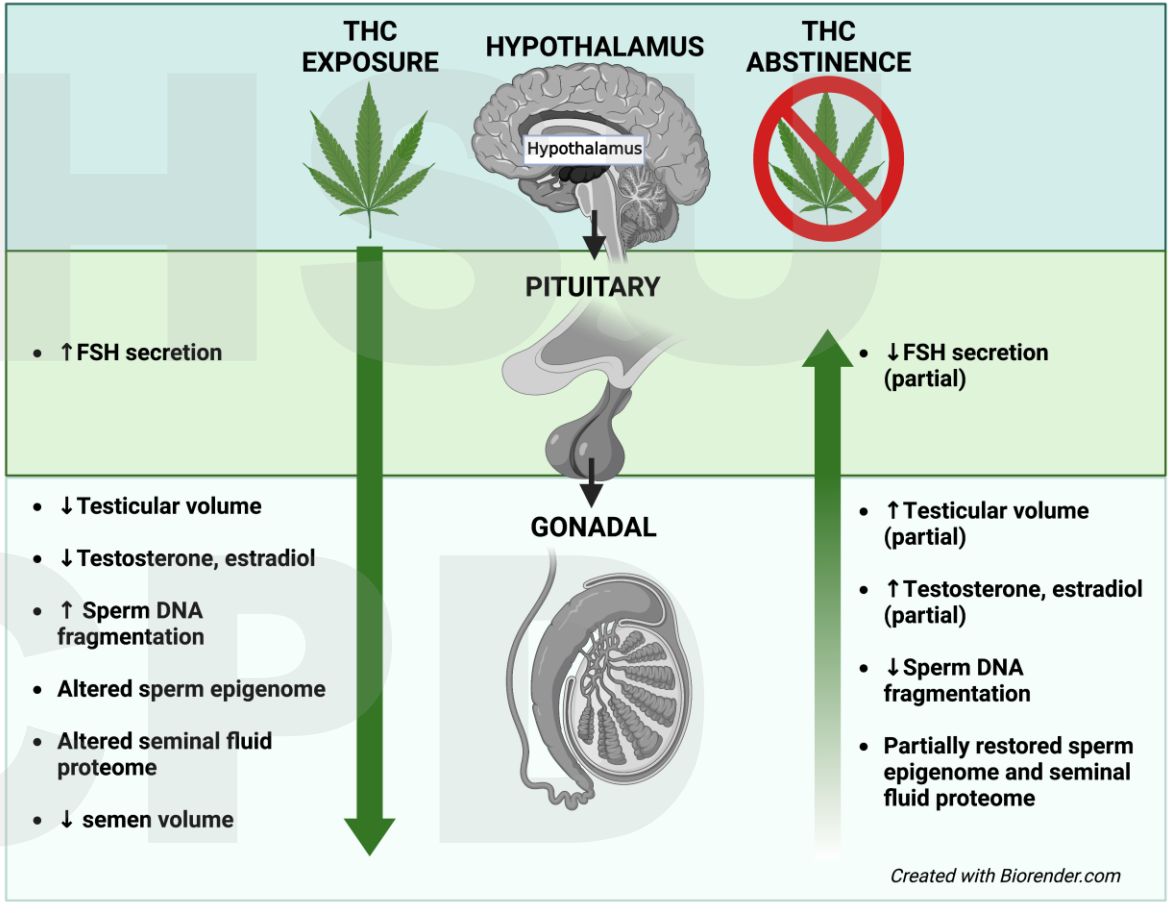
*P value < 0.05, **P value < 0.01 compared to never

Harlow – PRESTO Study (2021)

- 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

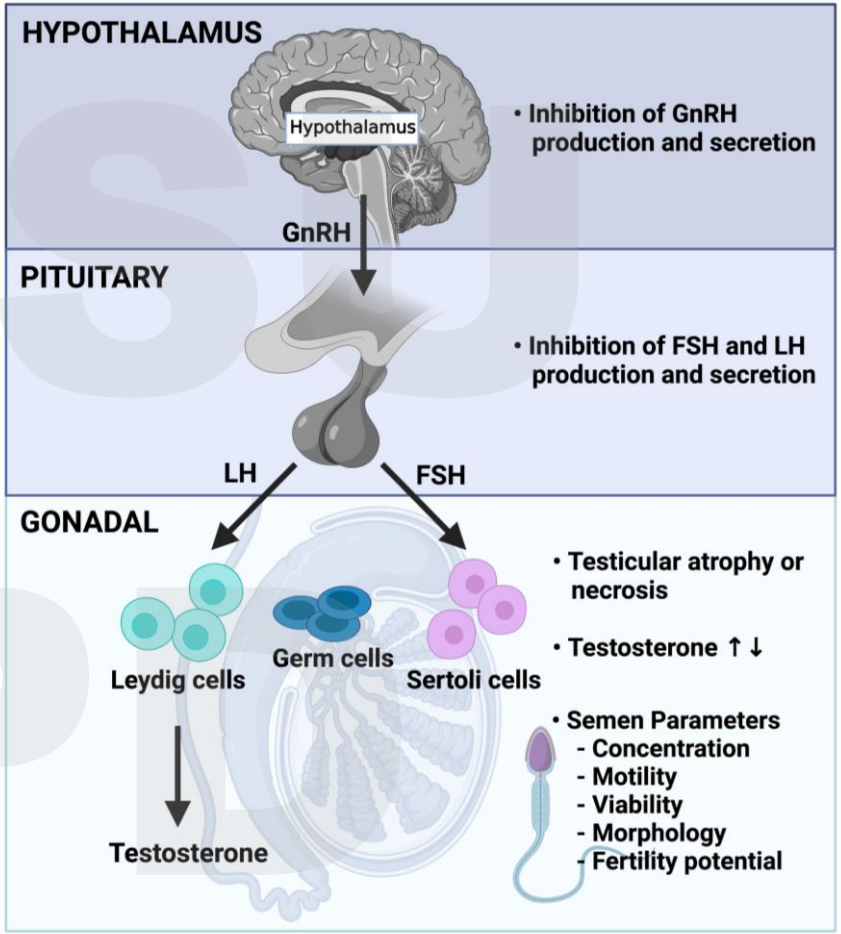
Possibility for recovery?

- 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



Cannabis and female reproductive health

Created with Biorender and statnews.com

Wise – The Fecundability Study (2018)

- 4,194 women large prospective population-based cohort study using online preconception monthly surveys

Frequent cannabis use was positively associated with:

- BMI
- Intake of alcohol and caffeine
- Perceived stress
- Depressive symptoms
- History of STIs
- Intercourse frequency
- Active and passive smoking
- Having a partner who uses cannabis

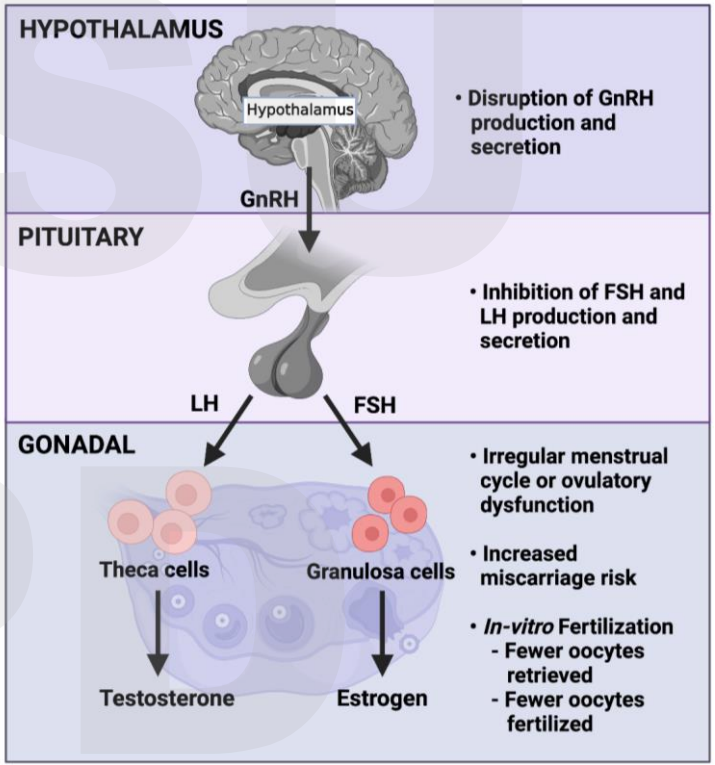
Chronic cannabis use was inversely associated with:

- Education
- Income
- Daily multivitamin use

Cannabis Use on Fertility

Prior human studies are limited by:

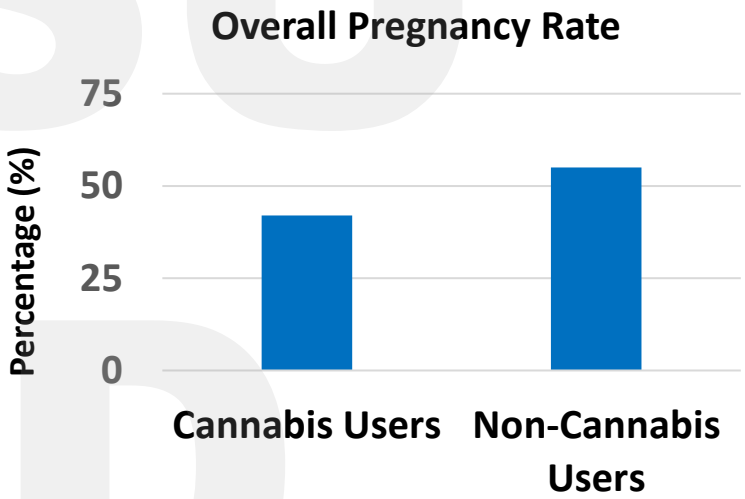
- Difficulty defining dose/exposure
- Polysubstance Use
- Non-physiologic route of ingestion



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

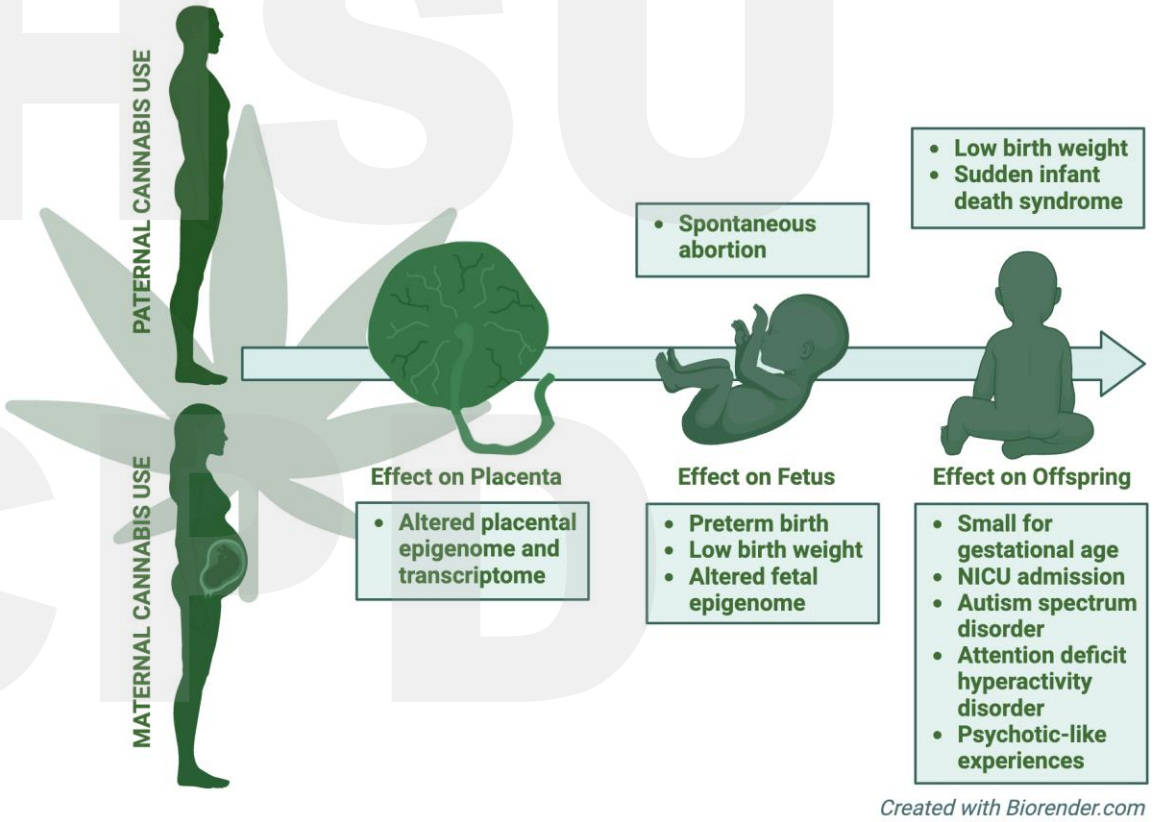
Take-Home Points

- 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

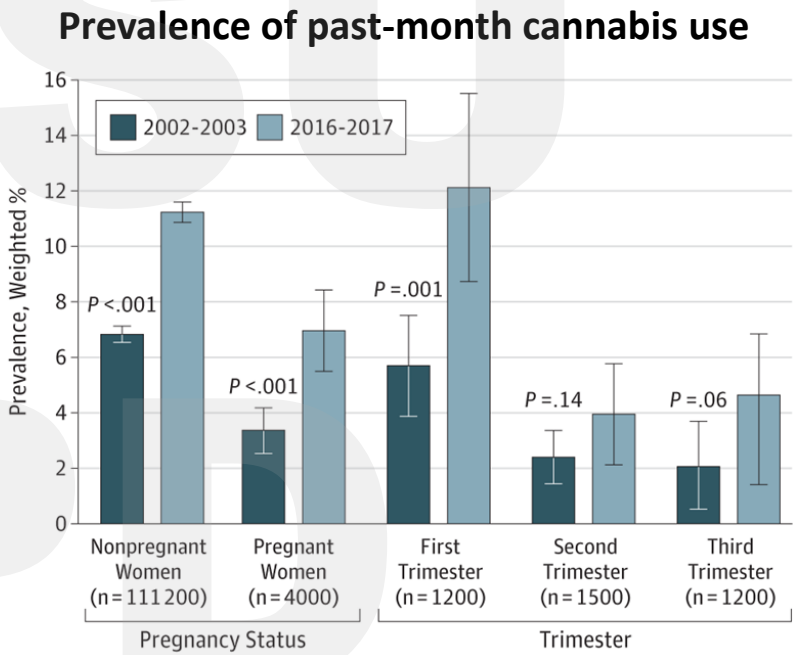
Preconception cannabis use and impact on offspring

- 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

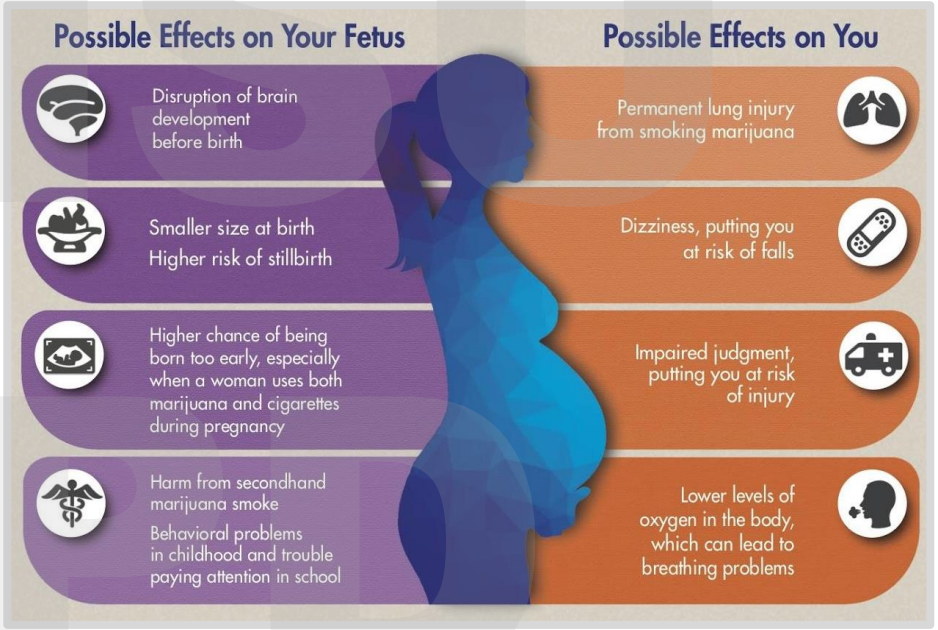
Outcomes of Prenatal Cannabis Exposure

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

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

References

- The National Survey on Drug Use and Health 2019, Substance Abuse and Mental Health Serices Administration
- Gundersen, T. D. et al. Association between use of marijuana and male reproductive hormones and semen quality: a study among 1,215 healthy young men. Am. J. Epidemiol. 182, 473–481 (2015).
- Thistle, J. E. et al. Marijuana use and serum testosterone concentrations among U.S. males. Andrology 5, 732–738 (2017).
- Gundersen TD, Jørgensen N, Andersson AM, Bang AK, Nordkap L, Skakkebæk NE, Priskorn L, Juul A, Jensen TK. Association Between Use of Marijuana and Male Reproductive Hormones and Semen Quality: A Study Among 1,215 Healthy Young Men. Am J Epidemiol. 2015 Sep 15;182(6):473-81. doi: 10.1093/aje/kwv135. Epub 2015 Aug 16. PMID: 26283092.
- Feiby L Nassan, Mariel Arvizu, Lidia Mínguez-Alarcón, Paige L Williams, Jill Attaman, John Petrozza, Russ Hauser, Jorge Chavarro, Marijuana smoking and markers of testicular function among men from a fertility centre, Human Reproduction, Volume 34, Issue 4, April 2019, Pages 715–723,
- Wise LA, Wesselink AK, Hatch EE, Rothman KJ, Mikkelsen EM, Sørensen HT, Mahalingaiah S. Marijuana use and fecundability in a North American preconception cohort study. J Epidemiol Community Health. 2018 Mar;72(3):208-215. doi: 10.1136/jech-2017-209755. Epub 2017 Dec 22. PMID: 29273628.
- J. C. Hedges, C. B. Hanna, J. C. Bash, E. R. Boniface, F. C. Burch, S. Mahalingaiah, V. H. J. Roberts, J. J. D. Terrobias, E. C. Mishler, J. V. Jensen, C. A. t. Easley, J. O. Lo, Chronic exposure to delta-9-tetrahydrocannabinol impacts testicular volume and male reproductive health in rhesus macaques. Fertil Steril 117, 698-707 (2022).
- Smith AMA, Ferris JA, Simpson JM, et al. Cannabis use and sexual health. J Sex Med 2010; 7(2 Pt 1):787 – 793.
- Sun AJ, Eisenberg ML. Association between marijuana use and sexual frequency in the United States: a population-based study. J Sex Med 2017; 14:1342 – 1347.
- Bhambhvani HP, Kasman AM, Wilson-King G, Eisenberg ML. A survey exploring the relationship between marijuana use characteristics and sexual function in men. Sex Med 2020; 8:436 – 445.
- Elbendary MA, El-Gamal OM, Salem KA. Analysis of risk factors for organic erectile dysfunction in Egyptian patients under the age of 40 years. J Androl 2009; 30:520 – 524.
- Pizzol D, Demurtas J, Stubbs B, et al. Relationship between marijuana use and erectile dysfunction: a systematic review and meta-analysis. Am J Mens Health 2019; 13:1557988319892464.