

Perinatal Marijuana Use

Nicole Fox, MD, MPA

Lead Psychiatrist, St. Luke's Health System

May 27, 2020



Weed and Pregnancy: How Cannabis Laws Are Hurting Mothers



Is It Okay to Smoke Pot During Pregnancy?

the Atlantic

Outline

- ◇ Epidemiology
- ◇ Why use marijuana?
- ◇ Marijuana Primer
- ◇ Cannabinoids
- ◇ Caveats
- ◇ Associations with gestation and development
- ◇ Breastfeeding
- ◇ Discussing MJ Use
- ◇ Hyperemesis Gravidarum vs Cannabinoid Hyperemesis Syndrome
- ◇ Helpful Resources





As of 1/2020, 33 states plus DC have legalized Medical Marijuana



10 states have legal recreational use



CDC estimates 16% of pregnant women ages 18-44 are daily consumers of MJ



Data points toward > risk of miscarriage, birth defects, and developmental delays

Epidemiology



Primer: Why use MJ?

- ◇ Belief that it is benign (not harmful)
- ◇ For fun, in social settings
- ◇ To alleviate psychiatric symptoms like depression, anxiety and insomnia
- ◇ Believe it is safer than SRIs and want to avoid conventional medication in pregnancy
- ◇ To help with morning sickness
- ◇ ...

Primer: Marijuana Use and Dosing

Marijuana is typically inhaled (smoked or vaped) or ingested as an “edible”

Delta-9 THC (aka THC) is the primary psychoactive component

THC levels in MJ are 25x that of the 1970s

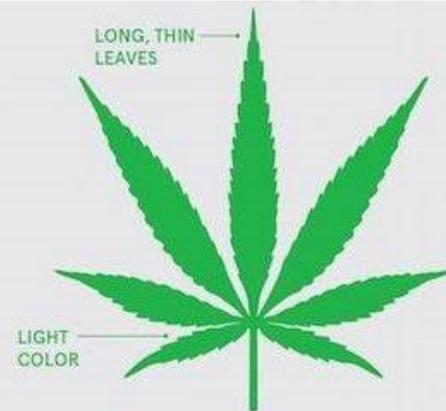
Inhalation

- rapid distribution of THC into the bloodstream and onset of effects
- Dose varies with strain, number, volume and depth of inhalations

Ingestion

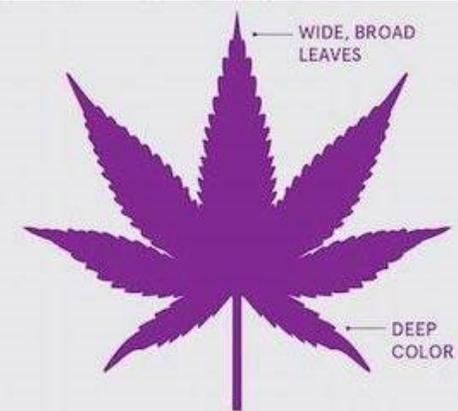
- slower onset of physiologic effects due to effects of first pass metabolism
- Dose easier to measure

WHAT STRAINS/ FORMULATIONS?



SATIVA

VS.

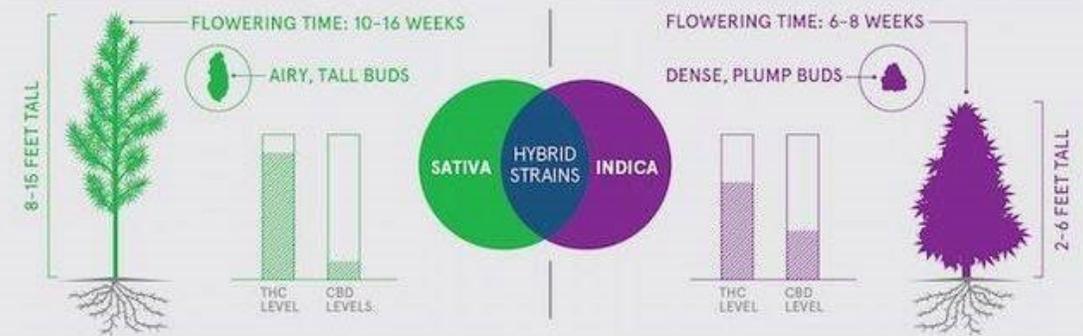


INDICA

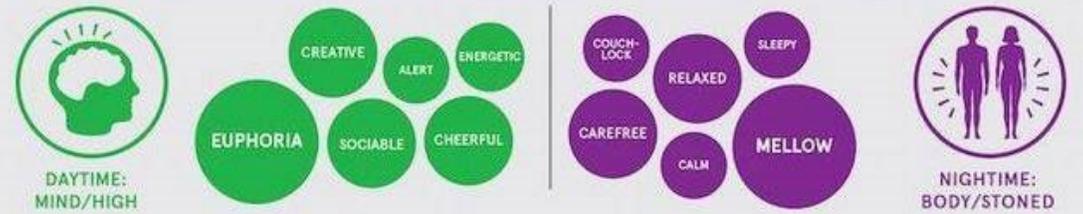


RUDERALIS is a short, hearty, wild strain with fewer leaves and low THC content. It is not used for consuming but is sometimes crossbred with indicas or sativas to produce an "autoflowering" hybrid—meaning it will produce flowers (buds) based on age rather than light cycles like sativas or indicas.

GROWING



EFFECTS



Primer: Metabolism of THC

THC has a half life of about 8 days in fat

Is highly lipophilic (fat loving)

Is detectable in the bloodstream for about 30 days

Once circulating, easily crosses the blood brain and placenta (brain is > 60% fat)

One study found THC in fetal blood in 15 minutes after consumption. At 3 hours, THC level in mother and fetus was at equilibrium.

Maternal tissue can act as a THC reserve and supply THC to fetal circulation after consumption

Cannabinoids

Endogenous Cannabinoid:
neurotransmitters produced
in the body which bind to
cannabinoid receptors in the
brain, immune system,
gonads and elsewhere

Anandamide is a prototypical
endogenous cannabinoid

Exogenous Cannabinoid:
most notable is the
phytocannabinoid,
tetrahydrocannabinol (delta
9- THC)

Cannabinoids

Cannabinoids act on 2 main types of G-coupled protein receptors, CB1 and CB2

CB1 receptors are highly expressed in the brain and gonads (testes and ovaries)

CB2 receptors are found more prominently in immune and some neuronal cells

Endogenous
Cannabinoids interact with receptors that tightly regulate elements of gestation and development

Exogenous Cannabinoids are likely partial agonists whose binding may have adverse downstream effects

If
cannabinoids
are naturally
occurring,
how can they
lead to
adverse
effects?



Endogenous production of cannabinoids is regulated and limited



Dosing of exogenous cannabinoids is additive to physiologic levels and may overwhelm systems that are normally closely regulated



Exogenous CB
potentially adversely
impacts:

Pre-implantation
Implantation
Embryo
Development

Caveat



Studying Marijuana use during pregnancy is difficult



Older data is generally less reliable due to much lower potency MJ in past



Can not complete randomized trials on pregnant women



We use animal models and generally extrapolate data to humans

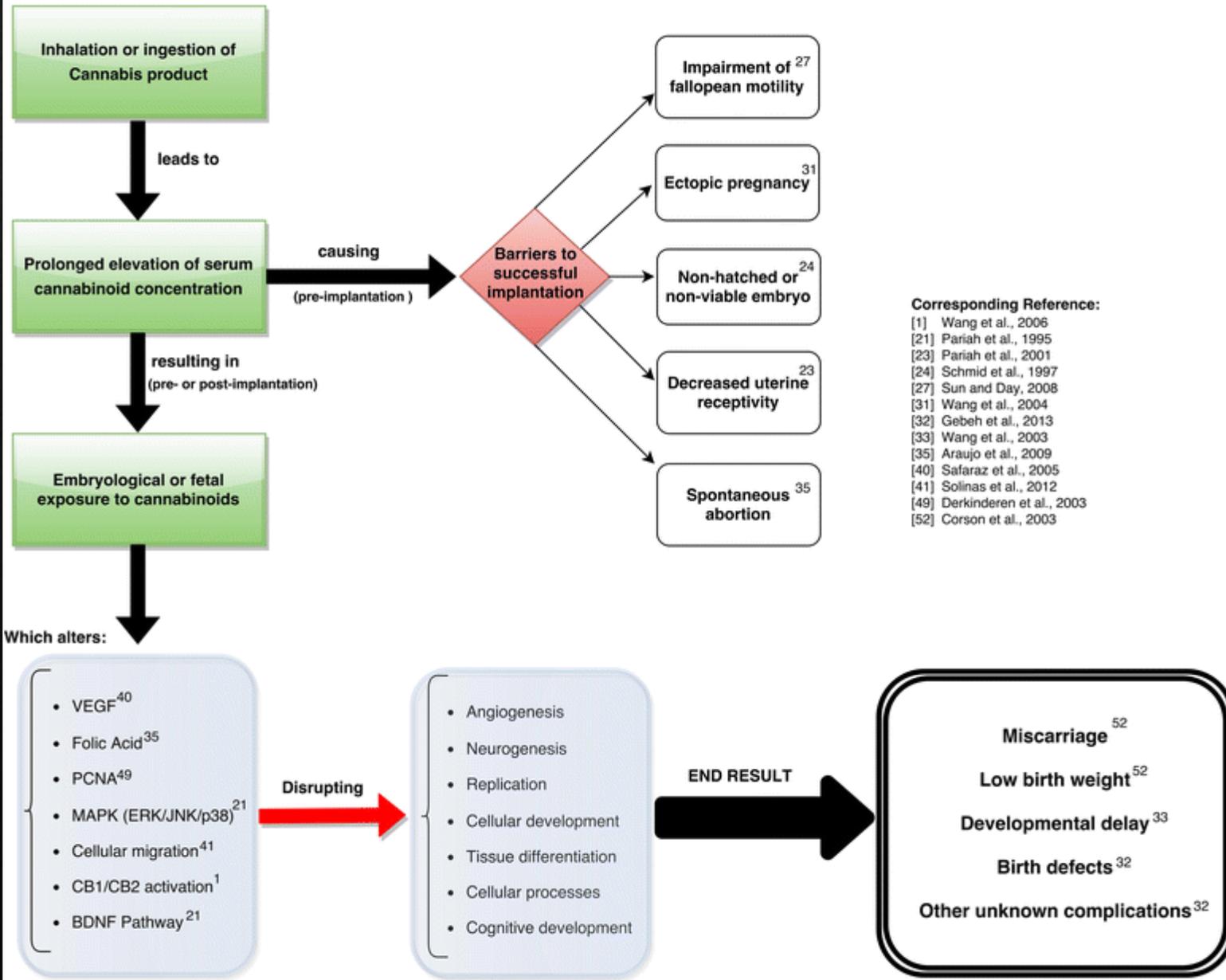


This is imperfect, but the best we have



Given imperfect data, advise avoidance or harm reduction model

Cannabinoids Endanger Fetal Development by Multiple Mechanisms



Corresponding Reference:

- [1] Wang et al., 2006
- [21] Pariah et al., 1995
- [23] Pariah et al., 2001
- [24] Schmid et al., 1997
- [27] Sun and Day, 2008
- [31] Wang et al., 2004
- [32] Gebeh et al., 2013
- [33] Wang et al., 2003
- [35] Araujo et al., 2009
- [40] Safaraz et al., 2005
- [41] Solinas et al., 2012
- [49] Derkinderen et al., 2003
- [52] Corson et al., 2003

From: The grass isn't always greener: The effects of cannabis on embryological development

Overview of cannabinoid action on fetal developmental mechanisms. A flowchart of the proposed mechanisms by which cannabis affects embryological and fetal development. Note that many "end result" outcomes were observed in animal models.

Pre- implantation

CB1 and CB2 receptors are present in the female reproductive system

These receptors are activated by endogenous anandamide and act as inhibitors

Inhibition can be overactivated by excess cannabinoid

Dose dependent increased signaling is associated with:

Developmental arrest
of the 2 cell embryo

Decreased blastocyst
viability

Decreased zona-
hatching

Inhibition of
implantation

Implantation

High levels of anandamide serves as a surrogate marker for elevated exogenous cannabinoid in some studies

Successful implantation depends on timely transport of the fertilized egg to the uterus

As cannabinoid concentration increases, transport of the fertilized egg becomes sluggish

Delayed transport increases risk of ectopic pregnancy (pregnancy outside of the uterus)

Anandamide levels in women with ectopic pregnancy are higher than controls with uterine pregnancies

Uterine Implantation may fail when blastocysts exposed to higher cannabinoid signaling level

Folic Acid aka vit B9

Must come from diet or supplements

Needed for normal development and growth of embryo and placenta

Is vital to DNA replication in dividing cells

THC interferes with fetal folic acid uptake from mother

Deficiency is associated with low birth weight, neural tube defects

Cellular Growth Factors

Cannabinoid signaling is involved with modulation of cell growth and angiogenesis (blood vessel development)

VEGF (vascular endothelial growth factor) is the most important factor in blood vessel development

Increased cannabinoid signaling reduces VEGF expression in a dose and time dependent manner

Decreased VEGF decreases otherwise tightly regulated vessel growth

Additionally, excess CB exposure induces apoptosis (planned cell death) across cell lines

Neuronal Development

Cannabinoids act on the CB1 receptor in the developing brain

Neural stem cells are precursor cells that can differentiate into neurons or glial cells during embryo development

Cannabinoids have a regulatory role in determining the fate of these neural cells

Disruption of normal homeostasis by excess cannabinoid changes expression and differentiation

May lead to impacts on learning, memory and other developmental processes like limb growth

More study is required to further understand this

Breastfeeding



THC IS DETECTED IN BREAST MILK BETWEEN 6 DAYS TO 6 WEEKS FROM CONSUMPTION



ONE STUDY ESTIMATED ABOUT 2.5% OF MOTHER'S THC DOSE IS INGESTED



POSSIBLE ASSOCIATION WITH MOTOR DEVELOPMENT WITH DAILY USE



NEWBORN PERIOD IS TIME OF RAPID BRAIN DEVELOPMENT; USE MAY RESULT IN HYPERACTIVITY, POOR COGNITIVE FUNCTION



CANNABINOID IS INVOLVED MILK PRODUCTION REGULATION; USE MAY DECREASE QUALITY AND QUANTITY

Conclusions from the Literature

Endogenous Cannabinoids play a key regulatory role in many processes of embryonic growth and development

Excess cannabinoid, either endogenous or exogenous THC disrupts homeostasis

Disruption to tightly controlled processes may lead to adverse outcomes leading to miscarriage, congenital malformation and / or learning disability

More study is needed, however a cautious approach is recommended

When discussing risk vs benefits with patients, there is no clear benefit

How to Discuss MJ Use

Approach

Curiosity, not judgment:

- What do you like about marijuana? What does it help with? Do you have any worries about it?

Ask

Symptoms they may be trying to manage:

- Do you find it helps your anxiety? Sleep? Has anything else helped?

Invite

Questions:

- Are there things you've heard about MJ use in pregnancy? Would you like any resources?

Offer

Science and normalization together:

- Some moms have asked if MJ is risky to baby.
- Recent studies have surprised everyone. It turns out there may be adverse effects. Some of them are...

TABLE 1

Proposed diagnostic criteria for cannabinoid hyperemesis syndrome

Essential feature

Long-term cannabis use

Major features

Severe cyclic nausea and vomiting

Resolution of symptoms with cannabis cessation

Relief of symptoms with hot showers and baths

Abdominal pain (epigastric and periumbilical)

Weekly use of marijuana

Supportive features

Age younger than 50

Weight loss greater than 5 kg

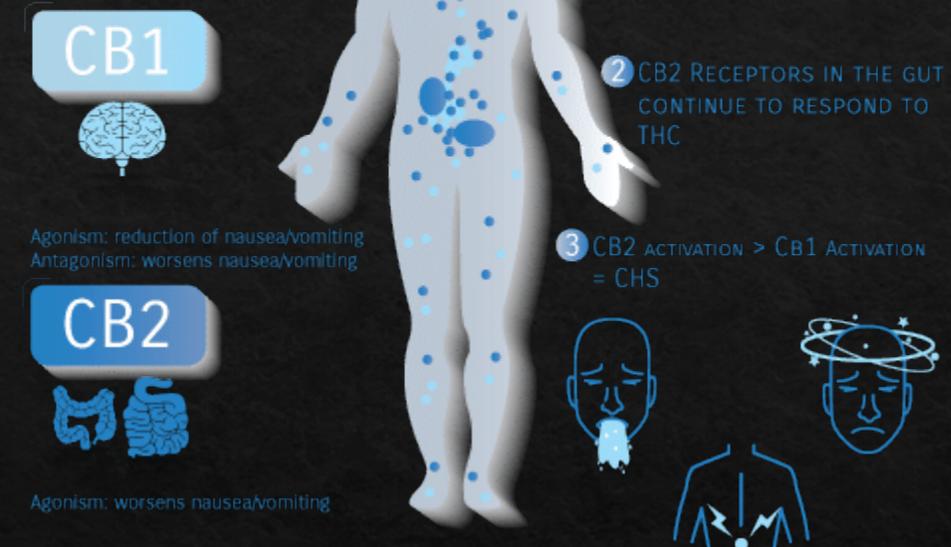
Morning predominance of symptoms

Normal bowel habits

Negative laboratory, radiographic, and endoscopic test results

Reprinted from Simonetto DA, Oxentenko AS, Herman ML, Szostek JH.
Cannabinoid hyperemesis: A case series of 98 patients.
Mayo Clin Proc 2012; 87:114–119,
Copyright 2012, with permission from Elsevier.

PATHOPHYSIOLOGY OF CANNABINOID HYPEREMESIS SYNDROME



Is it Hyperemesis Gravidarum or Cannabinoid Hyperemesis Syndrome?

Resources & References

Websites

- ◆ Centers for Disease Control and Prevention. “Marijuana use and Pregnancy.”
- ◆ HHS.gov. “Surgeon General’s Advisory: Marijuana Use and the Developing Brain.”
- ◆ Mothertobaby.org. “Marijuana”.
- ◆ MGH Center for Women’s Mental Health March 29, 2017. “The effects of Marijuana on Fetal Development.”

Pop Culture Articles

- ◆ Fox, Hayley. “Weed and Pregnancy: How Cannabis Laws Are Hurting Mothers.” *Rolling Stone Magazine* November 17, 2018.
- ◆ Nemo, Leslie. “Marijuana and Pregnancy: 5 Key Takeaways from the New Official Guidelines.” *LiveScience* August 27, 2018.
- ◆ Oster, Emily. “New Evidence on Pot During Pregnancy.” *The Atlantic* July 8, 2019.

Scientific References

- ◆ Colorado Department of Public Health. “Monitoring Health Concerns Related to Marijuana in Colorado” 2015.
- ◆ Corsi, D., Walsh, L., Weiss, D. “Association Between Self-reported Prenatal Cannabis Use and Maternal, Perinatal and Neonatal Outcomes.” *JAMA* 2019; 322(2):145-152.
- ◆ Friedrich, J., Khatib, D., Parsa, K. et al. “The grass isn’t always greener: The effects of cannabis on embryological development.” *BMC Pharmacoll Toxicol* 17, 45 (2016).
- ◆ Stanciu, Cornel. “An Overview of Cannabis Use in Pregnancy.” *Psychiatric Times* January 15 2020.

