Perinatal Marijuana Use

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Weed and Pregnancy: How Cannabis Laws Are Hurting Mothers

Is It Okay to Smoke Pot During Pregnancy?
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
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
- ...

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 crossed with indica or sativa to produce an "auto-flowering" hybrid—which means it will produce flowers (buds) based on age rather than light cycles like sativas or indicas.

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**GROWING**

- **FLOWERING TIME:** 10-16 weeks
- **TALL STRAINS:** 8-10 feet tall
- **INDIC STRAINS:** 4-6 feet tall

**HYBRID STRAINS**

**INDICA**
- **FLOWERING TIME:** 6-8 weeks
- **SHORT STRAINS:** 4-6 feet tall
- **RELAXED EFFECTS:**
  - **DAYTIME:** MIND/MILD
  - **EUPHORIA**: SOCIAL
  - **CAREFREE**: CHEERFUL
  - **NIGHTTIME:** BODY/STONED

**SATIVA**
- **FLOWERING TIME:** 10-16 weeks
- **TALL STRAINS:** 8-10 feet tall
- **CREATIVE EFFECTS:**
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**HYBRID STRAINS**

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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

**Primer: Metabolism of THC**
**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 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
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.
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:

<table>
<thead>
<tr>
<th>Developmental arrest of the 2 cell embryo</th>
<th>Decreased blastocyst viability</th>
<th>Decreased zona-hatching</th>
<th>Inhibition of implantation</th>
</tr>
</thead>
</table>
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
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.
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.

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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.
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**

<table>
<thead>
<tr>
<th>Essential feature</th>
<th>Long-term cannabis use</th>
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<tbody>
<tr>
<td><strong>Major features</strong></td>
<td>Severe cyclic nausea and vomiting</td>
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<tr>
<td>Resolution of symptoms with cannabis cessation</td>
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<tr>
<td>Relief of symptoms with hot showers and baths</td>
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<tr>
<td>Abdominal pain (epigastric and periumbilical)</td>
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<tr>
<td>Weekly use of marijuana</td>
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<td><strong>Supportive features</strong></td>
<td>Age younger than 50</td>
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<td>Weight loss greater than 5 kg</td>
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<td>Morning predominance of symptoms</td>
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<td>Normal bowel habits</td>
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<td>Negative laboratory, radiographic, and endoscopic test results</td>
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</tr>
</tbody>
</table>

Is it Hyperemesis Gravidarum or Cannabinoid Hyperemesis Syndrome?

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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”.

Pop Culture Articles

Scientific References