Marijuana Use in Pregnancy: & Some Colorado Experience

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Virginia Commonwealth University
Ware-Dunn Conference
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I have no COI to report

? “off-label” use of “medical therapeutics”

I have no personal experience with Colorado dispensaries. CUSOM has a “1 and done” policy if confirmed use from reported or suspected usage. Faculty are not subject to random screening for Marijuana.
Learning Objectives

- Marijuana epidemiology, legalization (Colorado and nationally)
- Pharmacokinetics of Marijuana
- Pitfalls of testing for marijuana use
- Risks of marijuana use in pregnancy and lactation
- Prevalent use before and after legalization and attitudes toward Marijuana use in Colorado
Marijuana Use in the U.S.

- Increase from 2007-2012
  - 14.8 million -> 19.8 million current users
  - 41% - 42.8% lifetime prevalence
- Self-reported
- Effects if de-stigmatized

Source: Substance Abuse and Mental Health Services Administration survey of the United States.
Reported Prevalence Rates in Pregnancy

- Most common *illicit* drug used in pregnancy

- *Self-reported* prevalence rates
  - 2-5% in most studies
  - 11-28% in young, high-risk, women from low socio-economic backgrounds
2016 Ballots for Legalization: Ma, Me, Ca, Nv, Az
Possible legislation: NH, Vt, RI, De, Md, DC, Hi
Ballot for Medical MJ: Ark, Fla, ND

23 red states, 4 Green states
7 red states, 9 green states
Colorado Laws

- 2000  Medical Marijuana Registry created
- 2008  First dispensaries opened
- 2012  Personal use of cannabis legalized
- 2017  >$1B in revenue, $130M in Tax revenue
(Non-Health) Challenges from Legalization in Colorado

- Banking laws - Largely cash business
- Federal banks reluctant to do business within industry
- Paying taxes - how to transfer funds
- Can not transfer or transport proceeds out of state (nor product)
- Real estate ownership may be limited for production and sales
- Laws are not clear and law enforcement inconsistent
- Guidelines for driving impaired not standardized
- Consumption laws confusing - where, when and what
TALKING TO YOUR PATIENTS: LAWS

If pregnant women report their substance use to their prenatal health care provider and/or have a positive drug test during a prenatal care visit, Colorado law prevents that information from being used in criminal prosecution. (C.R.S. § 13-25-136)

Tetrahydrocannabinol (THC), both recreational and medical, is considered a Schedule 1 drug under federal and Colorado law. (C.R.S. § 18-18-203)

Current Colorado law defines a baby testing positive at birth for a Schedule 1 substance (including recreational or medical THC or other drugs) as an instance of child neglect, which requires a report to social services. (C.R.S. § 19-3-102)

Please inform your patient: Marijuana is now legal for adults over 21. But this doesn't mean it is safe for pregnant moms or babies. Some hospitals test babies after birth for drugs. If your baby tests positive for THC at birth, Colorado law says child protective services must be notified.
What is Cannabis?

- Genus of flowering plant with medicinal and psychoactive effects (THC)

- THC=delta-9-tetrahydrocannabinol

- Small, lipophilic molecules that easily cross the blood-brain barrier

- Endogenous Cannabinoid receptors largely in the CNS, some organs and immune cells

- THC crosses placenta and is excreted in breast milk.
THC - MAJOR IN VIVO METABOLISM

Cannabinoid (CB) Receptors
Brain (CNS) → CB-1
Periphery → CB-2

Δ⁹-THC → 11-hydroxy-THC → 11-nor-9-carboxy-THC

pKa of 10.6, a ClogP computed as 5.34
octanol-water partition of 6000:1 at pH 7

THC → 11-OH-THC
CYP2C9 and 3A4

THC-Carboxy-Glucuronide
THC-Dicarboxylic acid
Pharmacokinetics of Marijuana

The graph illustrates the concentration of THC (tetrahydrocannabinol) and THC-COOH (tetrahydrocannabinolic acid) in the bloodstream over time. The lines show different exposure scenarios:

- **THC (single smoking exposure)**: shows a rapid increase and a quick decline.
- **THC-COOH (chronic)**: indicates a slower and more sustained increase.
- **THC-COOH (single oral exposure)** and **THC (single oral exposure)**: demonstrate different patterns of concentration increase and decrease compared to smoking.

The x-axis represents time (hours) since use, while the y-axis indicates concentration (ng/mL). The graph provides insights into how different methods of marijuana consumption affect the body's absorption and elimination of THC and its metabolites.
Testing Modalities

- **Saliva-** Parent compound, Short half-life, does not last long in saliva. Can be negative within a day.
- **Hair-** Marginal ICR for THC. False positives ?exposure
- **Urine-** (POC-Immunoassays) Quick, simple and relatively inexpensive. Can not test for metabolites and results vary depending on dosing, usage, habitus and metabolism. Can not determine level of impairment.
- **Serum-** (GC-MS) Most sensitive, more sophisticated and costly. Screen for multiple metabolites. Used for forensic analysis and confirmation. Better correlation of exposure.
How to Screen and Test

- ACOG:
  - Screen all patients at initial OB intake visit: Ask about substance use, alcohol and tobacco.
  - Encourage cessation and refer to treatment programs prn

- NO accurate way to quantify amount of THC ingested by testing in the clinical setting, timing of drug use nor route of consumption
Why Studying THC Use in Pregnancy is Hard

- Subjective report vs. biologic testing - Prevalence unknown
- Biologic testing result depends on timing, chronicity, body habitus, route of consumption, individual physiology or which metabolite
- Ethical issues of reporting maternal substance use in pregnancy or breastfeeding
- Concurrent substance use, especially tobacco, and socioeconomic factors confound results
- Difficulty of long-term follow-up for potentially affected children
Benefits to Marijuana Use?

- ? treatment for nausea & vomiting, aches & pains or anxiety. (Panacea for TOPs or MOPs ?)

- Roberson et al 2014. “Marijuana use and maternal experiences of severe nausea during pregnancy in Hawai’i.”
  - Severe nausea more prevalent in women using marijuana (3.7% vs. 2.3%)

- Westfall et al 2006. “Survey of medicinal cannabis use among childbearing women.”
  - 48% of those studied used marijuana for nausea/vomiting
  - 92% found this to be effective
What are the Potential Risks?

- Growth Restriction
- Fetal Malformations
- Stillbirth
- Preterm birth
- Neonatal Withdrawal
- Abnormal Neurodevelopment

- Mixed outcomes data, poor reproducibility, design flaws, reporting limitations, paucity of studies restrict conclusions
Marijuana Use and Fetal Growth

10 studies included

- Adjustments made for tobacco exposure
- Most studies used self-report not biologic testing
- Pooled OR 1.09 for LBW (<2500 g) amongst any use. (0.94-1.27)
- Heavy marijuana use (4x/wk) associated with average decreased fetal growth of 131g
Marijuana Use and Fetal Growth

Prospective growth ultrasounds
Self-reported marijuana use
Continued use during pregnancy 277 g decrease in birth wt.
Growth decreased by 8.9g/wk among fetuses with continuous exposure compared to fetuses no exposure (n=214)
Marijuana Use and Fetal Malformations

- No apparent association
- Multiple prospective studies
- Multiple retrospective cohort studies
- Limitations
  - Self report & Recall bias
  - Timing of exposure unclear
  - Limited quantification of exposure
  - Confounding variables- Substance abuse, Socio-economic, Diet, Domestic Abuse, General health and access to healthcare.
Marijuana Use and Stillbirth

Association Between Stillbirth and Illicit Drug Use and Smoking During Pregnancy

Michael W. Varner, MD,¹ Robert M. Silver, MD,¹ Carol J. Rowland Hogue, PhD,² Marian Willinger, PhD,³ Corette B. Parker, DrPH,⁴ Vanessa R. Thorsten, MPH,⁴ Robert L. Goldenberg, MD,⁵ George R. Saade, MD,⁶ Donald J. Dudley, MD,⁷ Donald Coustan, MD,⁸ Barbara Stoll, MD,¹,⁹ Radek Bukowski, MD,⁶ Matthew A. Koch, MD, PhD,⁴ Deborah Conway, MD,⁷ Halit Pinar, MD,⁸ Uma M. Reddy, MD, MPH,³ and for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network

- Case-control study from 3/2006-9/2008
- Biologic testing using umbilical cord blood
- Increased risk in women using marijuana: OR 2.34 (1.13-4.81)
- Effect was partially confounded by tobacco use
Marijuana Use and Preterm Birth

- Conflicting results
- Multiple prospective and retrospective studies
- Most show no increased risk
- Varying methodology
Marijuana Use and Preterm Birth

- SCOPE study- 5.6% reported MJ use prior or during pregnancy. (Smoking rate 26%)

- Continued MJ use through 20 wks 5X increase in SPTB

- In the group with SPTB
  - MJ use through 20 weeks Avg gestation <30 wks.
  - MJ >20 wks
    - 36%<28wks
    - 64%<32wks
  - Nonusers
    - 4.7%
    - 16%

Leemaqz SY. et al. Repro Tox, 2016;62:77
### Adverse Pregnancy Outcomes

#### Neonatal Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Any Marijuana Use (N=48)</th>
<th>No Marijuana Use (N=1562)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small for gestational Age</td>
<td>8.2</td>
<td>7.4</td>
<td>.83</td>
</tr>
<tr>
<td>Spontaneous PreTerm Birth</td>
<td>13.2</td>
<td>6.2</td>
<td>.08</td>
</tr>
<tr>
<td>Hypertensive Disorder</td>
<td>14.0</td>
<td>9.0</td>
<td>.28</td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>31.2</td>
<td>21.2</td>
<td>.13</td>
</tr>
<tr>
<td>Neonatal intensive care unit admission</td>
<td>16.91%</td>
<td>9.46%</td>
<td>.12</td>
</tr>
<tr>
<td>Composite neonatal morbidity or death</td>
<td>14.12%</td>
<td>4.47%</td>
<td>.0002</td>
</tr>
<tr>
<td>- Neonatal pulmonary morbidity</td>
<td>7.48%</td>
<td>3.66%</td>
<td>.14</td>
</tr>
<tr>
<td>- Necrotizing enterocolitis</td>
<td>0.41%</td>
<td>0.15%</td>
<td>.33</td>
</tr>
<tr>
<td>- Seizures</td>
<td>0.32%</td>
<td>0.08%</td>
<td>.28</td>
</tr>
<tr>
<td>- Retinopathy of prematurity</td>
<td>0.56%</td>
<td>0.59%</td>
<td>.95</td>
</tr>
<tr>
<td>- Neonatal infection morbidity</td>
<td>9.75%</td>
<td>2.39%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>- Anemia requiring blood transfusion</td>
<td>1.34%</td>
<td>0.71%</td>
<td>.24</td>
</tr>
<tr>
<td>- Neonatal surgery</td>
<td>0.3%</td>
<td>0.75%</td>
<td>.37</td>
</tr>
<tr>
<td>- Hyperbilirubinemia</td>
<td>0%</td>
<td>0.025%</td>
<td>---</td>
</tr>
<tr>
<td>- Neonatal neurological morbidity</td>
<td>1.37%</td>
<td>0.25%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Marijuana Use and Neonatal Withdrawal

- No significant withdrawal syndrome has been reported.

- No report of pharmacological treatment for cannabis withdrawal.

- Potential neurobehavioral disturbances:
  - Sustained startle reflexes
  - High-pitched cries
  - Sleep cycle disturbances
Impact on Long-Term Neurodevelopment

- Ottawa Prenatal Prospective Study (n=180)

<table>
<thead>
<tr>
<th>Age</th>
<th>Observed Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4years</td>
<td>No differences in behavior, intellect, visual perception, language, attention and memory tasks</td>
</tr>
<tr>
<td>&gt;4years</td>
<td>Increased behavioral problems, memory difficulties, weaker performance on tasks involving visual perception and language</td>
</tr>
<tr>
<td>9-12years</td>
<td>No difference in global IQ scores or visual task performance</td>
</tr>
</tbody>
</table>
### Impact on Long-Term Neurodevelopment

**Maternal Health Practices and Child Development Project**

<table>
<thead>
<tr>
<th>Age</th>
<th>Observed Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 years (n=655)</td>
<td>No differences</td>
</tr>
<tr>
<td>6 years</td>
<td>Decreased verbal reasoning</td>
</tr>
<tr>
<td>10 years (n=636)</td>
<td>Decreased attention, increased hyperactivity and impulsivity, Poorer reading and spelling performance</td>
</tr>
<tr>
<td>14 years (n=524)</td>
<td>Lower reading, math, spelling scores; Earlier age of onset of substance use</td>
</tr>
</tbody>
</table>
• IQ:
  o MODERATE evidence for association with decreased IQ scores, reduced cognitive function, and decreased academic ability in adolescence

• Behavior:
  o MODERATE evidence for association with attention problems
  o MIXED evidence for association with newborn behavior issues
  o LIMITED evidence for association with increased depression symptoms and delinquent behaviors
  o INSUFFICIENT evidence for association with psychosis symptoms
Still Birth
- LIMITED evidence for association with increased risk of stillbirth

Preterm Birth
- MIXED evidence for association with preterm delivery

Birth Weight
- MIXED evidence for association with decreased birth weight, and being born small for gestational age

Birth Defects
- MIXED evidence for association with birth defects; including neural tube defects and gastroschisis
- LIMITED evidence for association with heart defects
Marijuana Use During Lactation

- Newborn exposed to an estimated 0.8% of mother’s drug exposure.

- Difficult to separate effect of use in pregnancy from use during lactation.

- Currently AAP says breastfeeding is contraindicated.
What’s Happening at CU?

- Prevalence of Cannabis use in Early Pregnancy Prior to and after Legalization in Colorado

- Approved by Colorado Multiple Institutional Review Board as Quality Improvement Project
Methods: Post-Legalization Cohort

- Prospective cohort study (Mar-Sept, 2015)
- De-identified urine samples from new Ob patient visits tested for cannabinoid metabolites with Medimpex© THC Marijuana Drug Test Urine Cassettes
- Privately-insured patients from Faculty and Midwifery clinics; publicly-insured patients from Resident and Midwifery clinics
- Test results (+/-) and clinic of origin recorded
## Demographics of New Obstetric Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=400</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median (range) or %</td>
</tr>
<tr>
<td></td>
<td>29 (18-46)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>45.5%</td>
</tr>
<tr>
<td>Black</td>
<td>16.3%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20.8%</td>
</tr>
<tr>
<td>Other</td>
<td>17.4%</td>
</tr>
<tr>
<td>Gravida</td>
<td>2 (1-11)</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (0-8)</td>
</tr>
</tbody>
</table>
Clinics from which samples were obtained

- Private (Faculty/Midwives) 65%
- Public (Resident/Midwives) 35%

N=308
Results

Marijuana prevalence

Public (Resident/Midwives) 13.8%
Private (Faculty/Midwives) 7.0%

p=0.05
OR 2.1 (1.0-4.6)
N=308
Methods: Pre-Legalization Cohort

- Pre-Legalization Cohort
  - Pts invited to participate in a prospective longitudinal registry and bio-banking protocol “Baby Blanket” supported by CCTSI (Colorado Clinical and Translational Science Award) funded via NIH
  - From March 2011 – December 2013 Plasma samples collected during early PNC
  - Plasma analyzed LC/MS for Δ9THC and other metabolites.
## Positive Test Results: Baby Blanket Prior to Legalization

<table>
<thead>
<tr>
<th>THCpos</th>
<th>Count</th>
<th>Public</th>
<th>Private</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Count</td>
<td>128</td>
<td>153</td>
<td>281</td>
</tr>
<tr>
<td></td>
<td>% within clinicPrivate</td>
<td>91.4%</td>
<td>95.6%</td>
<td>93.7%</td>
</tr>
<tr>
<td>1.0</td>
<td>Count</td>
<td>12</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>% within clinicPrivate</td>
<td>8.6%</td>
<td>4.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>140</td>
<td>160</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>% within clinicPrivate</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Conclusions

- Post Legalization more likely to test +  1.5 (0.8-2.8)
- Public vs. Private use Pre and Post  2.1 (1.1-3.6)
Conclusions

- Marijuana use is more prevalent in our patient population than has been reported in previous studies—particularly after legalization of recreational marijuana.

- Marijuana use is more prevalent in publicly-insured patients than in privately-insured patients.
Limitations

- Initial Ob intake visits
- Relatively small sample size
- Difference in the sensitivity of the testing used in the Pre-legalized cohort vs. post-legalization.
What do Our Patients Believe about Marijuana Use in Pregnancy?

PROJECT #2

COLLABORATORS:
ALLISON REID BURKS, HAYLEY CROSSMAN,
SARAH BLACK, DR. MARY KOHN,
JEANELLE SHEEDER, PHD
Methods

- Prospective cohort study
- March – December, 2015
- Anonymous survey distributed to all pregnant patients at 3 University of Colorado clinics
- Results stored in RedCap
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (% or range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 (18-43)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>63%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21%</td>
</tr>
<tr>
<td>Black</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Highest Education Level</strong></td>
<td></td>
</tr>
<tr>
<td>Undergraduate Degree</td>
<td>34%</td>
</tr>
<tr>
<td>Graduate Degree</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Relationship Status</strong></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>63%</td>
</tr>
<tr>
<td>Single</td>
<td>37%</td>
</tr>
</tbody>
</table>
Results: Self-Reported Marijuana Use

- 5% Currently using marijuana
- 12% Used in the month prior to pregnancy
- 83% No marijuana use
Results: Knowledge, Attitudes, and Beliefs

Women believe marijuana alleviates common ailments:

- Helps with stress (n=103): 54% Strongly Agree or Agree, 20% Neither Agree or Disagree, 12% Strongly Disagree or Disagree, 4% Don’t Know / No Opinion
- Takes away aches and pains (n=101): 58% Strongly Agree or Agree, 20% Neither Agree or Disagree, 12% Strongly Disagree or Disagree, 4% Don’t Know / No Opinion
- Helps with headaches (n=103): 48% Strongly Agree or Agree, 20% Neither Agree or Disagree, 12% Strongly Disagree or Disagree, 4% Don’t Know / No Opinion
- Takes pain away (n=103): 56% Strongly Agree or Agree, 20% Neither Agree or Disagree, 12% Strongly Disagree or Disagree, 4% Don’t Know / No Opinion
- Helps with anxiety (n=103): 40% Strongly Agree or Agree, 20% Neither Agree or Disagree, 12% Strongly Disagree or Disagree, 4% Don’t Know / No Opinion
Results: Knowledge, Attitudes, and Beliefs

Women are unsure what effects marijuana can have on a baby

- Can reach a baby through the placenta (n=100) 49%
- Can cross into breast milk (n=100) 42%
- Can affect the brain of a baby (n=101) 51%
- Can affect a baby's development (n=101) 47%
- Can lead to a smaller baby (n=101) 58%
Conclusions

- Knowledge is lacking in the general public, even in highly educated populations.

- We need to do a better job educating ourselves and our patients.
Thank You

• Jeanelle Sheeder, MSPH, PhD  Ob/Gyn Peds
• Jane Limmer, MD  Ob/Gyn
• Laura Borgelt, PharmD  Pharm
• Michael Wempe, PhD  Pharm
References

- Fried, PA. The Ottawa Prenatal Prospective Study (OPPS): Methodological Issues and Findings – It’s Easy To Throw the Baby Out with the Bath Water. Life Sci 1995;56:2159-68.
References