Weeding Out the Myths: Marijuana in Pregnancy and Lactation

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Disclosures

Dr. Borgelt reports no relevant financial relationships.

Dr. Borgelt will be discussing unapproved drugs and unapproved uses for drugs.

Dr. Borgelt has served as a member of five working groups:
- Colorado Department of Public Health and Environment: Amendment 64 (Marijuana Legalization) Task Force Working Group: Consumer Safety and Social Issues
- State Licensing Authority Labeling, Packaging, Product Safety and Marketing
- State Licensing Authority Medical and Retail Marijuana Mandatory Testing and Random Sampling
- State Licensing Authority Serving Size and Product Potency
- Colorado Department of Public Health and Environment Public Health Advisory
Objectives

- Describe the prevalence of cannabis use in the pregnant population
- Determine the impact of marijuana on the fetus and newborn infant
- Explain the effects of in utero marijuana exposure on long-term growth and neurodevelopment
- Provide recommendations regarding marijuana use in pregnancy and lactation
POLL QUESTION

I live in a state that has enacted medical marijuana laws.

1. Yes
2. No
POLL QUESTION

I know someone who is pregnant or breastfeeding that is using marijuana for medical or recreational purposes.

1. Yes, medical purposes
2. Yes, recreational purposes
3. Yes, both
4. No
Patient Case

- The medical resident presents to the medical team the following case:
- 26 year-old female presenting to clinic for well-child check of her 3 month old infant. Mother is breastfeeding.
- No tobacco use, minimal alcohol use, smoking marijuana one to two times daily.
- Mother and baby doing well.
- Medical resident told the mother it was “completely fine” to smoke marijuana while breastfeeding as there were no adverse effects.
Marijuana

- Single molecule pharmaceuticals
  - Dronabinol (Schedule III)
  - Nabilone (Schedule II)

- Liquid extract: nabiximols (Sativex®)
  - Approved in 24 countries; U.S. - Phase III trials

- Phytocannabinoid-dense botanicals
  - *Cannabis sativa* – medicinal plant (Schedule I)
Cannabis

- Plant-derived cannabinoids
  - $\Delta^9$-tetrahydrocannabinol - THC
  - $\Delta^8$-tetrahydrocannabinol - THC
  - Cannabidiol – CBD
  - Cannabinol - CBN
  - Cannabigerol - CBG
  - Cannabichromene - CBC
  - Cannabicyclol
  - Cannabiisoin
  - Cannbitriol
  - Miscellaneous
  - Cannabinodiol (air-oxidation)
Cannabis Use in Pregnancy

- Self reports of 4-5% with estimates ranging from 2.5-27%

Study of 100 low-income, primarily African-American postpartum women

<table>
<thead>
<tr>
<th>Past 3 weeks</th>
<th>Past 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report</td>
<td>Toxicology</td>
</tr>
<tr>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Sources:
- BJOG 2002;109:21-7
- Drug Alcohol Rev 2011;30:181-7
- Drug Alcohol Depend 2010;109:243-7
Cannabis Continuation in Pregnancy

- 86 women in UK
- Interview data
  - Lifetime use
  - Year before pregnancy
  - Month before pregnancy
  - Three trimesters
- Various backgrounds

Conclusion: 60% of cannabis users continued to use ~10 joints/week throughout pregnancy (60-70% of the level of use the year before)
Medicinal Cannabis Use in Women

Survey: results from 79 of 84 women using medicinal cannabis
In British Columbia, Canada

- 65% Used Cannabis
- 68% Didn't Use Cannabis

Surveyed women: 79 out of 84 in British Columbia, Canada.
Case Report: The Other Side of the Coin

- 26 yr old female presents to University Women’s Hospital Basel
- 10th week gestation with N/V for past 24 hours
- PMH: hospitalization 4 months ago due to gastritis-like symptoms with N/V, terminated pregnancy 7 years ago
- SH: smokes 5 cigarettes/day; no other drug use or meds
- Hyperemesis gravidarum assumed
- Hospital course:
  - Day 1: Frequent and severe vomiting episodes (up to 12 times a day) and nearly constant nausea; resistant to vitamin B6, metoclopramide, chlorazine, dexamethasone, and ondansetron
  - Day 2: patient showered more than once a day and her constitution and mood seemed to considerably improve during and shortly after showering
  - Specific inquiry: regular daily use of cannabis since 13 yrs; stopped smoking after learning about pregnancy 10 days ago
- Symptoms improved with hot showers and baths up to 5 times per day

CANNABINOID HYPEREMESIS SYNDROME
Which of the following receptors is a key target for THC?

1. Cannabinoid-1 receptor (CB1)
2. Cannabinoid-7 receptor (CB7)
3. Peroxisome Proliferator-Activated Receptor (PPAR)
4. G-protein receptor 55 (GPR55)
Endocannabinoid System

- Endocannabinoids and their receptors found throughout body: brain, organs, connective tissues, glands, and immune cells.
- In each tissue, the cannabinoid system performs different tasks; goal is always **homeostasis**
- Endocannabinoids are substances our bodies make naturally to stimulate CB1 and CB2
  - Anandamide
  - 2-arachidonoylglycerol (2-AG)
- When cannabinoid receptors are stimulated, a variety of physiologic processes occur
  - CB1 receptors: nervous system, connective tissues, gonads, glands, organs
  - CB2 receptors: immune system and associated structures
- Exogenous cannabinoids stimulate CB1, CB2 and others

Endocannabinoid System
Cannabis Pharmacology

http://www.tokeofthetown.com/2011/03/worth_repeating_bodys_own_cannabinoids_are_the_bli.php
Endocannabinoid System

14 WEEKS
Marijuana’s Effects on the Brain

When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.
Cannabis Exposure During Pregnancy

- Potential for supra-physiological stimulation of endogenous cannabinoid system
  - Disrupt endocannabinoid signaling
  - Interfere with synaptogenesis (formation of synapses in CNS)
  - Interfere with development of neuronal interconnections
    - Axon development and growth impaired

- Disruption of developing neurotransmitter systems
  - Disrupts tyrosine hydroxylase activity (rate limiting enzyme for dopamine synthesis)
  - Alter precursors for the expression of opioid and serotonin receptors (in animal models)
Several potential mechanisms exist through which prenatal cannabinoid exposure may exert its impact.
How Should MJ Be Studied?

A. Blog
B. Case control study
C. Case report
D. Case series
E. Cohort study
F. Meta-analysis
G. My opinion
H. Randomized controlled trial
I. Review article

“HIGHEST” level of evidence

“LOWEST” level of evidence
# Three Prospective Longitudinal Studies

<table>
<thead>
<tr>
<th>STUDY AND INVESTIGATOR</th>
<th>INITIATION DATE AND LOCATION</th>
<th>POPULATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ottawa Prenatal Prospective Study (OPPS) Fried, et al.</td>
<td>1978 Ottawa, Canada</td>
<td>Low-risk, European-American, middle-class; Exposure to marijuana and cigarettes</td>
</tr>
<tr>
<td>Maternal Health Practices and Child Development Study (MHPCD) Day, et al.</td>
<td>1982 Pittsburgh, Pennsylvania</td>
<td>High-risk, mixed ethnicity (57% African American), single (71%), low socioeconomic status; Exposure to marijuana and alcohol</td>
</tr>
<tr>
<td>Generation R Study Hoffman, et al.</td>
<td>2001 Rotterdam, Netherlands</td>
<td>Multi-ethnic, higher socio-economic status</td>
</tr>
</tbody>
</table>

# Fetal Development and Birth Outcomes

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Fetal Development and Birth Outcome</th>
</tr>
</thead>
</table>
| OPPS                       | Gestational age reduced  
No differences in birth weight                                        |
| MHPCD                      | Birth length reduced after first trimester exposure only  
Increased birth weight after third trimester exposure                     |
| Generation R Study         | Fetal growth reduced from second trimester onwards  
Reduced birth weight                                                      |

*Other studies have also demonstrated conflicting results:  
Low birth weight, preterm labor, small for gestational age, admission to NICU  
(Pediatric Research 2012;71:215-9)  
No difference in birth weight, shorter birth length, smaller head circumference  
(BJOG 2002;109:21-7)
# Neonatal Development

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Neonatal development</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPPS</td>
<td>Increased startles and tremors</td>
</tr>
<tr>
<td></td>
<td>Reduced habituation to light</td>
</tr>
<tr>
<td>MHPCD</td>
<td>No differences in neonatal behavior</td>
</tr>
<tr>
<td></td>
<td>Subtle differences in EEG sleep recordings (subsample)</td>
</tr>
<tr>
<td>Generation R Study</td>
<td>Not examined</td>
</tr>
</tbody>
</table>

# Infant Behavior

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Infant Behavior</th>
</tr>
</thead>
</table>
| OPPS                | 12/24 months: no differences in BSID scores  
36 months: more advanced motor skills  
48 months: lower memory functioning and verbal scores (heavily cannabis–exposed) |
| MHPCD               | 9 months: lower BSID scores (heavily cannabis-exposed)  
19 months: no differences in BSID scores  
36 months: lower short-term memory functioning and verbal reasoning (only in African-American offspring) |
| Generation R Study  | 18 months: more aggression and inattention for exposed girls only  
30 months: no differences in non-verbal cognition scores or vocabulary development  
36 months: no differences in behavior for both sexes |

*BSID: Bayley Scales of Infant Development*
# Child Behavior and Cognitive Development

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Child Behavior and Cognitive Development</th>
</tr>
</thead>
</table>
| OPPS        | 6 years: more impulsivity and hyperactivity  
9-12 years: impaired visuo-perceptual functioning  
13-16 years: abstract designs latency, poor Peabody spelling performance, poor attention stability (heavy cannabis-exposed); lack of association with IQ and verbal memory |
| MHPCD       | 6 years: more impulsivity, hyperactivity, delinquency; detrimental effect on intellectual development (heavy cannabis-exposed)  
10 years: more impulsivity, hyperactivity, inattention; delinquency; more problems in abstract and visual reasoning; depressive symptoms if exposed in first/third trimester  
14 years: delinquency, less school achievement (heavy cannabis-exposed)  
16 years: slower processing speed and reaction time |
<p>| Generation R| Not yet examined                                                                                                                                                                                                                         |</p>
<table>
<thead>
<tr>
<th>STUDY</th>
<th>Young Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPPS</td>
<td>18-22 years: prenatal exposure to marijuana impacts upon neural activity in brain regions that are responsible for response inhibition.</td>
</tr>
<tr>
<td></td>
<td>18-22 years: prenatal marijuana exposure alters neural functioning during visuospatial working memory processing.</td>
</tr>
<tr>
<td>MHPCD</td>
<td>Not yet examined</td>
</tr>
<tr>
<td>Generation R</td>
<td>Not yet examined</td>
</tr>
</tbody>
</table>
Limitations of Studies

- Concurrent use of other substances
- Confounding factors
  - Environmental risk factors
  - Family history
  - Maternal IQ/cognitive ability
  - Socioeconomic status
  - Recruitment methods
- Measures of illicit drug use (e.g., self-report)
- Assessment measures
- Loss of subjects over time
LUNGS
Vaporized or Smoked
Organic material, hash, hash oil

GUT
Oral Ingestion
Lipophilic, alcoholic, supercritical fluidic extracts of plant material

SKIN
Topical Application
Creams, buccal tinctures made from plant extracts

http://www.bestvaporizers.com/marijuana-vaporizers.html
http://www.health.harvard.edu/blog/teens-who-smoke-pot-at-risk-for-later-schizophrenia-psychosis-201103071676
Potency of Marijuana

Potency of Seized Marijuana in the U.S.

121% increase from 1998-2010

Average Potency (% THC Content)

Source: University of Mississippi, National Center for Natural Products Research, Potency Monitoring Project Quarterly Report 115 (December 2011)

MHPCD initiation
## Summary of Prenatal Marijuana Exposure

### Short-term effects/birth outcome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>Mixed evidence</td>
</tr>
<tr>
<td>Low birth weight/SGA</td>
<td>Mixed evidence</td>
</tr>
<tr>
<td>Fetal growth</td>
<td>Mixed evidence</td>
</tr>
<tr>
<td>Anomalies</td>
<td>Mixed evidence</td>
</tr>
<tr>
<td>- Gastroschisis</td>
<td></td>
</tr>
<tr>
<td>- Ventricular septal defect</td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>No effect</td>
</tr>
<tr>
<td>Neurobehavior</td>
<td>Effect</td>
</tr>
</tbody>
</table>

### Long-term effects

<table>
<thead>
<tr>
<th>Domain</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior/attention</td>
<td>Effect</td>
</tr>
<tr>
<td>Cognition</td>
<td>Effect</td>
</tr>
<tr>
<td>Language</td>
<td>No effect</td>
</tr>
<tr>
<td>Achievement</td>
<td>Effect</td>
</tr>
</tbody>
</table>
## Summary: Human and Animal Studies

<table>
<thead>
<tr>
<th>Prenatal</th>
<th>Neonatal</th>
<th>Infant</th>
<th>Child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced fetal growth</td>
<td>Decreased birth weight</td>
<td>Impaired mental development (9 mo)</td>
<td>Increased hyperactivity (6 and 10 yrs)</td>
<td>Altered functioning in visuo-spatial memory (18-22 yrs)</td>
</tr>
<tr>
<td>Reduced head circumference</td>
<td>Altered gestational length</td>
<td>Increased aggression and inattention in girls (18 mo)</td>
<td>Impaired abstract and visual reasoning (10 yrs)</td>
<td></td>
</tr>
<tr>
<td>Increased pulsatility and resistance index of uterine artery</td>
<td>Increased startles and tremors</td>
<td>Impaired memory function (36-48 mo)</td>
<td>Impaired visuoperceptual functioning (9-12 yrs)</td>
<td></td>
</tr>
<tr>
<td>Decreased inner diameter of aorta</td>
<td>Reduced abitation to light</td>
<td>Decreased verbal scores (36-48 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placental resistance</td>
<td>Altered EEG sleeping recordings</td>
<td>Increased anxiety and depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axonal bundle malformation</td>
<td>Decreased birth weight</td>
<td>Increased rearing and locomotor activity at P15-20</td>
<td>Altered open field performance</td>
<td>Memory impairment at P40-80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity at P12</td>
<td>Impaired consolidation of long-term memory at P22</td>
<td>Reduced synaptic plasticity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Learning impairment at P10-12</td>
<td>Inhibited social interaction and play behavior</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased ultrasonic vocalization at P10</td>
<td></td>
<td>Altered social behavior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impaired synapse formation</td>
<td></td>
<td>Anxiogenic-like profile</td>
</tr>
</tbody>
</table>

Marijuana and Breastfeeding

- THC excreted into human milk in moderate amounts
- Relative Infant Dose: 0.8%
- Milk:plasma ratio is 8:1 (chronic, heavy users)
- Animal studies show MJ could inhibit lactation
  - Inhibiting prolactin production
  - Direct action on the mammary glands
- Two studies in women who smoked while breastfeeding
  - No differences were noted in outcomes on growth, mental, and motor development
  - Slight decrease in infant motor development at one year, especially when used during the first month of lactation
- Infants will test positive in urine screens for 2-3 weeks

Marijuana Labeling: Colorado

“There may be additional health risks associated with the consumption of this product for women who are pregnant, breastfeeding, or planning on becoming pregnant.”
Recommendations

1. Ask about the use of marijuana and consider screening in high-risk patients
2. Educate women about impact of cannabis during pregnancy and lactation and strongly advise discontinuation or use harm-reduction approach
3. Offer drug services/counseling and/or cognitive behavioral therapy
4. Perform appropriate developmental milestones
5. Counsel about patient safety issues including keeping out of the reach of children and using proper packaging and labeling of marijuana
6. Avoid second hand/passive exposure
7. Follow hospital policies and procedures
Conclusions

- Marijuana most likely used more frequently than reported in pregnancy and lactation
- Potential mechanisms exist for marijuana to impose negative effects in brain development
- Although inconsistent, clinical studies indicate prenatal exposure to heavy marijuana use has:
  - Mixed effects in early infancy
  - Some specific cognitive or behavioral outcomes in childhood
  - Altered executive function in adolescence
- Marijuana should be regarded as harmful to the developing fetus and breastfeeding infant
THANK YOU!

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