Marijuana in Pregnancy: Sorting through the Hazy Evidence

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Learning Objectives
• Define prevalence of marijuana use in pregnancy and reported reasons for use.
• Counsel women regarding the risks of marijuana use during pregnancy and lactation based on current evidence.
• Recommend and utilize available on-line resources when counseling women regarding marijuana use in pregnancy and lactation.

Background- Marijuana
• Most common illicit drug used in pregnancy
• Crosses the placenta
• Anticipate increased use with increasing legalization of recreational marijuana

Background- Marijuana
• Current:
  • 33 states legalized for medicinal use
  • 10 for recreational use
• 2019:
  • NY, NJ, CT, IL, MN, NH, VT (rec)
  • SC, KS, WI, PA, TX (med)
• 2020
  • AZ, FL, OH, ND (rec)
  • MS, NE, SD (med)

https://www.profitconfidential.com/marijuana/list-us-states-marijuana-legal/
What is Marijuana?
• Cannabis sativa plant
• Contains over 600 chemicals compounds (cannabinoids)
  • Tetrahydrocannabinol (THC): psychoactive component
  • Cannabidiols: sedative, therapeutic effect
• Modes of consumption
  • Smoking
  • Vaping
  • Eating
  • Topical (lotions)

Smoking vs Edibles
• Smoking
  • Faster onset 5-15 minutes
  • Effect lasts 1-3 hours
• Edibles
  • Slower onset 30 minutes-1 hour
  • Peak effect anywhere from 1-6 hours
  • Increased ED visits and toxicity from edible products with high concentrations of THC

Marijuana Use in Pregnancy
• Reported prevalence 3-30% in pregnancy (self report vs biologic sample)
• Anonymous survey of women coming in for OB care- marijuana in past 30 days
  • 9.6% of women at DH
  • 10.7% of women at UH
• Self-report likely underestimates prevalence of use

Prevalence of Marijuana Use
• National Surveys on Drug Use and Health
  • Cross sectional, nationally representative survey
• 2014
  • 3.9% of pregnant women used in last month
• 2002
  • 2.4%

Increased Use with Legalization
• Retrospective cohort - Sept/Oct 2013 vs Sept/Oct 2014

Increased Use with Legalization?
• Data from the US Drug Testing Laboratories
• Compared Colorado meconium lab results to other states without legalization over same time period (1st 9 months 2012 and 2014)
• Increase by 10% in THC positive samples in CO consistent with rest of country
• However, concentration of THC in CO samples increased
  • THC mean 213 ng/g pre- and 361 ng/g post-legal
WIC Survey of Marijuana Use

• Tricounty Health Department (CO) survey
• Women participating in Special Supplemental Nutrition Program for Women Infant and Children (WIC)
• Monthly caseload of 25,000 clients
• Convenience sample with in-person surveys at 10 WIC offices
  • English and Spanish versions

1,749 women completed the survey (60.2% response rate)

• Among women who had ever used marijuana, 11% used marijuana during pregnancy
  • Only 3% used while breastfeeding
• Among women currently using marijuana, 36% used marijuana during pregnancy
  • Only 14% used while breastfeeding

Perceived Benefits WIC Survey

<table>
<thead>
<tr>
<th>Reasons for Use</th>
<th>Ever Users (%, n)</th>
<th>Current Users (%, n)</th>
<th>Past Users (%, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Help with depression/anxiety/stress</td>
<td>35% (164)</td>
<td>63% (60)</td>
<td>28% (103)</td>
</tr>
<tr>
<td>Help with pain</td>
<td>29% (135)</td>
<td>60% (57)</td>
<td>21% (78)</td>
</tr>
<tr>
<td>Help with nausea/vomiting</td>
<td>23% (108)</td>
<td>48% (46)</td>
<td>17% (62)</td>
</tr>
<tr>
<td>For fun/recreation</td>
<td>59% (277)</td>
<td>39% (37)</td>
<td>65% (240)</td>
</tr>
<tr>
<td>Other reason</td>
<td>16% (75)</td>
<td>14% (13)</td>
<td>16% (58)</td>
</tr>
</tbody>
</table>

Perceived Benefits

• Roberson et al
  • Women who used marijuana in pregnancy were more likely to report severe nausea (3.7 vs 2.3%, prevalence ratio 1.63, 95% CI 1.08-2.44)
• Westfall et al
  • 51% who used marijuana to treat nausea and vomiting of pregnancy and 92% of them felt it was effective
  • Effect of marijuana use on nausea and vomiting of pregnancy is unknown

Increasing Perceived Safety

• National Survey on Drug Use and Health data

<table>
<thead>
<tr>
<th>Year</th>
<th>No past 30 day use, pregnant</th>
<th>No past 30 day use, non-pregnant</th>
<th>Past 30 day use, pregnant</th>
<th>Past 30 day use, non-pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>3.5%</td>
<td>3.1%</td>
<td>25.8%</td>
<td>23.7%</td>
</tr>
<tr>
<td>2015</td>
<td>16.5%</td>
<td>14.8%</td>
<td>65.4%</td>
<td>62.6%</td>
</tr>
</tbody>
</table>

Methods of Testing for Use

• Urine
  • 2-3 days occasional and weeks in chronic user
• Meconium
  • Use 2nd trimester onward
• Hair
  • Passive exposure
• Serum
  • 2-3 days
Cord Homogenate vs Meconium

- Meconium may be more sensitive than cord homogenate testing
- 7 paired (collected from the same birth) cord and meconium samples
- Concentrations in cord lower for all analytes
- THCA was the most commonly detected analyte for both sample types

Problems with Existing Studies

- Lack of quantification/timing of exposure
- Difficulty adjusting for tobacco, other drugs, sociodemographic factors
- Reliance on self-report
- Shiono et al (1995) completed a prospective cohort study with structured interviews and maternal serum toxicology screens
- 70% of women with positive THC on serum tox screen denied use in structured interview

Outcome: Fetal Growth Restriction

- DATA ARE MIXED
- Meta-analysis (English et al 1997) focused on association between marijuana exposure and birth weight
- Women who consumed marijuana > 4 times per week had babies that weighed less than non-users by 131 grams on average
- However, pooled odds ratio for low birth weight with any marijuana use was 1.09 (95% CI 0.94-1.27)

Outcome: Fetal Growth Restriction

- Generation R study assessed fetal growth by ultrasound
- Fetuses exposed to cannabis in early pregnancy (n=214) grew 11.2 grams/week less than non-users
- Fetuses exposed to cannabis throughout pregnancy (n=41) grew 14.4 grams/week less than non-users
- Only study using ultrasound to assess fetal growth rather than using neonatal birth weight
**Outcome: Preterm Birth**

- DATA ARE MIXED
- Australian cohort (N=24,874) who self-reported MJ use at prenatal care intake
  - MJ use was associated with preterm birth (OR 1.5, 1.1-1.9)
- Second study ICD-10 codes for substance use
  - Increased incidence of preterm birth among MJ users (18.8% vs 5.8%)
- ALSPAC (N=12,129) preterm birth rate same among users and non-users (4.6% both groups)


**Outcome: Preterm Birth**

- Only 31% of women with a positive serum screen self-reported marijuana use in a structured interview
- Conversely only 43% of women who self-reported use had a positive serum screen
- No association with PTB with self-report and/or serum screen positive
  - Serum positive for THC associated with PTB (OR 1.3, 95% CI 1.0-1.7)


**Outcome: Preterm Birth**

- Saurel-Cubizolles (n=13,545)
  - 1% prevalence of use
  - Any marijuana use associated with SPTB (OR 2.15, 95% CI 1.10, 4.18)
- Dekker (n=3,184)
  - 7% marijuana-exposed by self-report in structured interviews
  - Pre-pregnancy use associated with SPTB with intact membranes (OR 2.34, 95% CI 1.22, 4.52)

Saurel-Cubizolles et al BJOG 2014, Dekker et al PLOS One 2012

**Outcome: Stillbirth**

- DATA ARE LIMITED
- Case-control study by Stillbirth Collaborative Research Network
  - Association between stillbirth and marijuana use as demonstrated by cord homogenate positive for THC (OR 2.34, 95% CI 1.13-4.81)
  - Adjusting for cotinine in the maternal serum to account for tobacco use reduced the stillbirth OR for marijuana by approximately 10%

Varner Obstet Gynecol 2014

**Outcome: Congenital Anomalies**

- DATA ARE LIMITED AND MIXED
- Linn et al 1983 found no association with major malformation (OR 1.36, 95% CI 0.97-1.91)
- Large retrospective cohort studies based on birth defects registries
  - Incomplete ascertainment of confounding factors
  - Potential for recall bias
- Currently not adequate evidence that marijuana exposure is associated with any specific congenital birth defect


**Outcome: NICU Admission**

- Warshak et al 2015 retrospective cohort
  - N=6468 women
  - 6,107 non-users
  - 361 marijuana users (self-report or positive tox screen)
- Increased risk of NICU admission
  - 12.5% vs 17.2% (aOR 1.54, 95% CI 1.14-2.07)

Warshak et al J Perinatol 2015
SCRN Secondary Analysis

- Secondary analysis singleton live births from SCRN database (N=1610)
- Marijuana use 2.7% live births
- Primary composite adverse pregnancy outcome HTN, stillbirth, SGA and SPTB similar users and non-users
  - 31.2% vs 21.2% (p=0.14)
  - aOR 1.29 (95% CI 0.56—2.96)

Outcome: Neonatal Morbidity

- Composite morbidity aOR 3.11 (95% CI 1.40-6.91)

Perinatal Outcomes Meta-Analysis

- Gunn et al conducted a systematic review and meta-analysis
  - Primary Outcomes: maternal, fetal or neonatal up to 6 weeks postpartum after cannabis exposure
  - Conducted meta-analyses when 3 or more studies available with same outcome (anemia, LBW, BW, neonatal length, NICU admission, GA at del, head circumference, PTB)
  - Increased odds anemia, LBW, NICU admit
  - More studies needed

Neonatal Outcomes: Meta-Analysis

- Conner et al performed systematic review and meta-analysis
  - Aim: estimate if marijuana use increases risk of adverse neonatal outcomes
    - Primary outcomes: LBW (<2500gm), PTB (<37 wk)
    - Secondary outcomes: BW, GA at delivery, SGA, level II nursery or greater, stillbirth, SAB, low Apgar, abruption, perinatal death
**Summary Meta-Analyses**

**Neurodevelopment**
- Alterations in neurotransmitters in rat models
  - Especially dopaminergic pathways
- Postmortem human fetal brains (elective terminations 17-22 weeks)
- Dopamine receptors reduced in marijuana-exposed fetuses
- Most prominent effect in males
- Directly correlated with amount of marijuana used during pregnancy


**Prospective Longitudinal Studies**

<table>
<thead>
<tr>
<th>STUDY AND INVESTIGATOR</th>
<th>INITIATION DATE AND LOCATION</th>
<th>STUDY SIZE (N)</th>
<th>POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ottawa Prenatal Prospective Study (OPPS), Fried et al</td>
<td>1978 Ottawa, Canada</td>
<td>180</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>1992 Pittsburgh, Pennsylvania</td>
<td>636</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>2002 Rotterdam, Netherlands</td>
<td>9778</td>
<td>Multi-ethnic, higher socioeconomic status</td>
</tr>
</tbody>
</table>


**Summary of Outcomes**

<table>
<thead>
<tr>
<th>Moderate evidence</th>
<th>Limited evidence</th>
<th>Insufficient evidence</th>
<th>Mixed evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased growth</td>
<td>Stillbirth</td>
<td>Psychosis symptoms</td>
<td>Preterm delivery</td>
</tr>
<tr>
<td>Decreased IQ scores in young children</td>
<td>SIDS (evidence of no association)</td>
<td>Initiation of future marijuana use</td>
<td>Decreased birth weight</td>
</tr>
<tr>
<td>Decreased cognitive function</td>
<td>Increased depression symptoms</td>
<td>Newborn behavior issues</td>
<td></td>
</tr>
<tr>
<td>Decreased academic ability</td>
<td>Delinquent behavior</td>
<td>Breastfeeding and infant motor development</td>
<td></td>
</tr>
<tr>
<td>Attention problems</td>
<td>Isolated simple ventricular septal defects</td>
<td>Birth defects, including NTD, gastroeschisis</td>
<td></td>
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<tr>
<td>Frequency of use during adolescence</td>
<td></td>
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Breastfeeding

- THC passes to the neonate in breastmilk
- Letter to the editor NEJM of two patients
  - Estimated exposure 0.8% of maternal exposure to one joint
  - Chronic heavy users up to 8x plasma

Perez-Reyes NEJM 1982

Breastfeeding

- Observational study of 8 women
  - Purchased product with known concentration of THC
  - Abstained from use for 24 hrs prior
  - Inhaled cannabis then collected breast milk at 20 minutes, 1, 2 and 4 hours
  - Exclusively breastfed infant ingest mean of 2.5% of maternal dose

Baker Obstet Gynecol 2018

Breastfeeding

- 54 samples from milk donors
  - Delta-9-THC detectable 63% samples up to 6 days after last reported use
  - Median concentration 9.47 ng/mL
  - Number of daily uses and time from sample collection to analysis were predictors of THC concentration in breastmilk

Bertrand et al Pediatrics

Breastfeeding

- Astley et al (1990) assessed neurodevelopment in babies who were exposed via breastmilk
  - Exposed infants scored poorly on Psychomotor Developmental Index compared to non-exposed
  - Unable to separate from prenatal exposure
  - 84% of women who used while pregnant continued while breastfeeding

Astley Neurotoxicol Teratol 1990

Breastfeeding AAP Statement

- American Academy of Pediatrics (AAP)
  - "Marijuana Use During Pregnancy and Breastfeeding"
  - Present data are insufficient to assess the effects of exposure of infants to maternal marijuana use during breastfeeding. As a result, maternal marijuana use while breastfeeding is discouraged.


ACOG Committee Opinion

- Women should not use marijuana during pregnancy or while lactating
  - Ob-gyns should not prescribe for medicinal purposes to pregnant or lactating women
  - Insufficient evidence for effects on nursing infant

ACOG, Committee Opinion No. 637, Marijuana Use During Pregnancy and Lactation, Obstet Gynecol 2015
How are we doing now?

• Holland et al. recorded patient encounters and evaluated obstetric provider response to disclosure of marijuana use
• 90/460 (19%) reported MJ use at OB intake
• 47 different health care providers
• 48% of the time provider did not respond to MJ disclosure
• When discussed, response non-specific and focused on tox screens and social services

Holland et al., Obstet Gynecol 2016

How are we doing now?

• “…You know how it alters your mind when you have it, how it makes you feel, so think about what it is doing to the baby that is not even formed quite yet. It gets the effects as well. And we don’t want to do that to the baby.”

Holland et al., Obstet Gynecol 2016

How are we doing now?

• “Um….the issue with marijuana specifically is just that it is illegal. So at the time of delivery, they will do a urine drug test because you have a history of using it. If it is positive, at the time of delivery, they will often have you, like force you to talk to child protective services because it is a risk factor.”

Holland et al., Obstet Gynecol 2016

Dispensary Project

• Mystery shopper study (400 randomly selected dispensaries)
• Caller was 8 weeks pregnant with nausea
• Nearly 70% had product recommendations
  • Predominantly recommended edibles
  • 65% based recommendation on personal opinion
  • Only 32% recommended discussion with healthcare provider without prompting

Dickson et al, Obstet Gynecol 2018

Guidelines for Providers

• colorado.gov/cdphe/marijuana-clinical-guidelines

Talking about Marijuana with Patients

Marijuana Pregnancy and Breastfeeding Clinical Guidance
Marijuana and Your Baby Factsheet
What do we tell patients?

• No known benefits of marijuana use in pregnancy
• Possible risks of marijuana use in pregnancy
• Advise patients not to use marijuana during pregnancy
• No known “safe” amount of marijuana in pregnancy

Where do we go from here?

• More research needed
  • Biologic sampling critical
  • Timing and quantification of exposure
  • Additional areas of investigation
    • Congenital malformations
    • Maternal morbidity
    • Neonatal morbidity (NICU admission)

References

• Ferguson SM, Horwood LJ, Mactavish E. Prenatally exposed children, with a special emphasis on cannabis exposure. Life Sci. 2002;70(23):2162-2168.
• Fried MA. The Ottawa Prenatal Prospective Study [OPPS]: methodological issues and findings--it's easy to throw the baby out with the bath water. Acta Obstet Gynecol Scand. 2014;121(8):971-987.

References


Thank you!