

The current evidence of benefits and risks pertaining to the use of marijuana and its derivatives, both medically and recreationally.

Ben Holland, MD

ACMEC Grand Rounds

June 13, 2018

Introduction

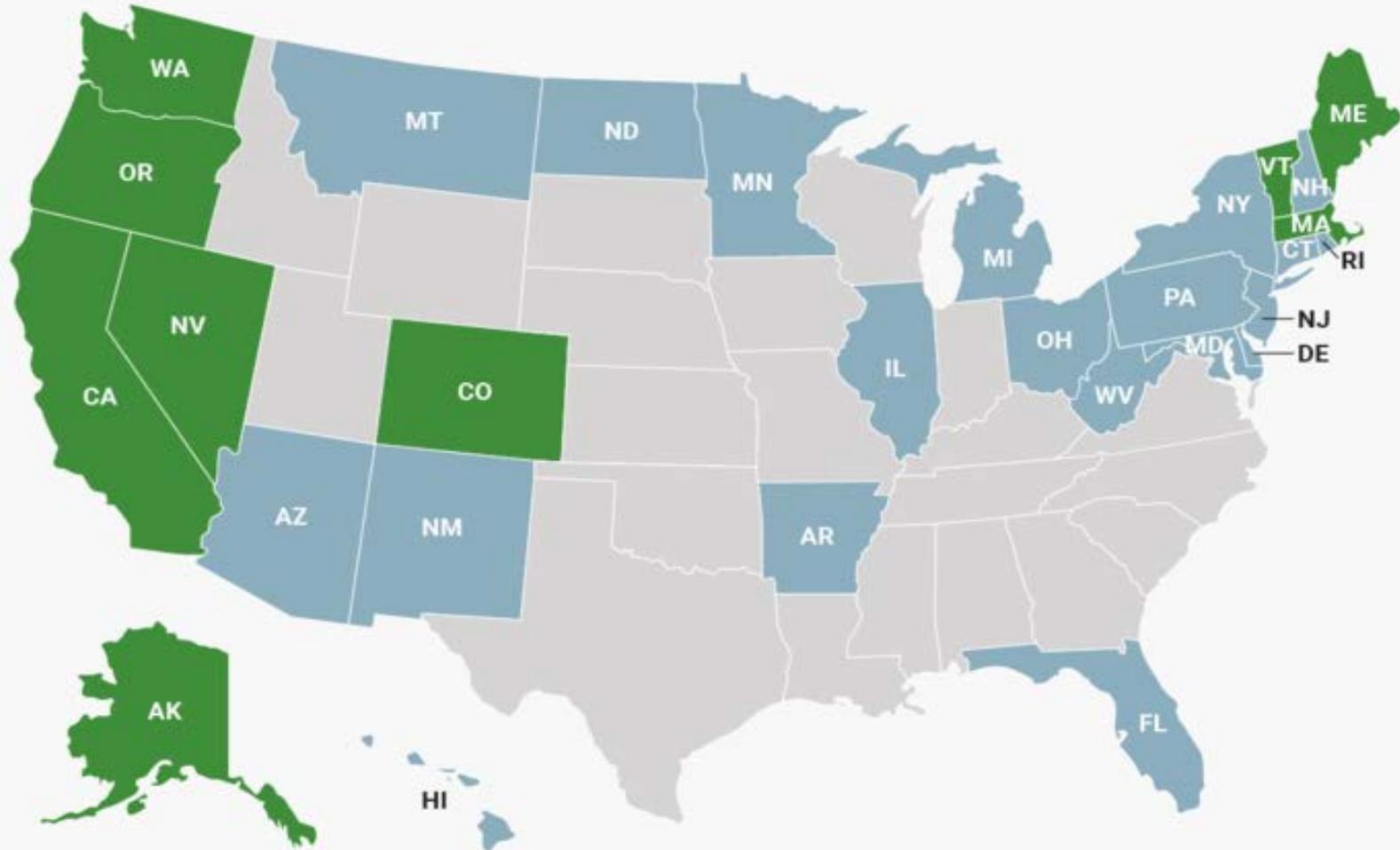
- Reason for addressing this topic: We are surrounded by states with legalized medicinal and recreational marijuana and its derivatives.
 - Many in Idaho are using these substances, though they remain illegal here. While illegality is an obvious issue, how else should patients be counseled, from an evidence based standpoint?
 - Could these substances be beneficial for certain patients? Are there severe risks to be mindful of? What are the reasons patients are using, and is there evidence supporting why they use?

Legalization of Marijuana

- States with legalized recreational use (laws vary by state regarding possession, growth, distribution, etc.):
 - Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, Vermont, Washington, Washington DC.
 - 28 states with medical legalization.
- common/societal perception: that marijuana is harmless when used recreationally and is an excellent medical treatment for many conditions.
- Risks are often not discussed in media, may be unknown to users.

States where marijuana is legal

■ Legalized recreational and medical marijuana ■ Legalized medical marijuana



BUSINESS INSIDER

Basics

- Genus *Cannabis*, various species.
- *Cannabis* has been used for its medicinal and psychotropic properties for thousands of years.

Endocannabinoid System

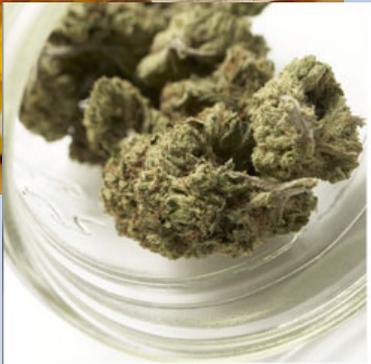
- Endocannabinoid system: throughout the CNS and PNS, also other tissues. Involved in homeostasis of various systems, sleep, concentration, memory, reward, cognition, pleasure, appetite, stress response/reduction, and modulation of pain and inflammation.
- also noted to affect neuronal development in animal studies.
- Cannabinoid receptors discovered in 1980s (CB1 and CB2). Most prevalent in hippocampus, cerebellum, amygdala, prefrontal cortex.

Phytocannabinoids

- The active substances in *Cannabis* plants.
- >420 chemical compounds in *Cannabis* plant. 61 are cannabinoids.
- More than 150 known compounds in *Cannabis* smoke.
- Most commonly known/studied cannabinoids are delta-9 Tetrahydrocannabinol (THC) and Cannabidiol (CBD).
 - THC: Primary psychoactive substance. THC content in Cannabis plants increasing over last 30 years.
 - CBD: complexes differently than THC with cannabinoid receptor and does not have the same psychotropic activity.

How is *Cannabis* being used?

- Various formulations and methods of intake: smoked, edible, oils, tinctures, oral whole plant extract, nabiximols (CBD-THC purified mixture)
 - Nabiximols is approved for use in Canada as an analgesic and muscle relaxant
- Synthetics: dronabinol (oral synthetic THC), nabilone (synthetic cannabinoid compound)
 - dronabinol is FDA approved chemotherapy induced nausea and vomiting, and appetite stimulation in AIDS.
 - nabilone is FDA approved for severe, refractory nausea and vomiting



<https://fivethirtyeight.com/features/marijuana-edibles-are-a-gamble-for-users/>

<https://420evaluationsonline.com/health-and-news/guidelines-for-dosing-with-medical-cannabis--routes-of-administration>

Timing and effects

- Approximately 2 to 3 mg of inhaled THC is sufficient to produce drug effects in a naïve user. How much per inhalation depends on strain of *Cannabis* used.
 - Onset of psychoactive effects occurs rapidly with peak effects felt at 15 to 30 minutes and lasting up to four hours
- Cannabis ingestion has a delayed onset of psychoactive effects that ranges from 30 minutes to three hours. Clinical effects may last up to 12 hours
 - In naïve users, psychotropic effects occur with 5 to 20 mg of ingested THC
 - Most prepackaged edible products contain about 4x the recommended dose per use of 10 mg THC.

Discussion of benefits and risks of use of *Cannabis* and cannabinoids

- The following is based primarily on the NASEM report regarding the therapeutic affects of *Cannabis* and cannabinoids, published January 2018, and the 2018 WHO report on the effects of nonmedical cannabis use.

Benefits

- **Chronic Pain:**
 - 5 fair to good systematic reviews. One review with 28 RCTs found cannabinoids to be beneficial in alleviating chronic pain. Most of these trials investigated whole plant extract, nabiximol, 5 looked at smoked or vaporized Cannabis plant material.
 - 17 of the trials looked at neuropathic pain alone.
 - NASEM concluded conclusive or substantial benefit.
 - Most studies did generally suggest improved pain control (up to 30-40%) reduction in pain vs control, but most of these generally failed to reach statistical significance.
 - Recent open-label study of medicinal cannabis for patients with chronic pain showed improvement in pain, but also 44% of those on opioids had discontinued their opioids at the end of the 6 month study period. (Fitzcharles). No discussion on QOL or adverse effects, though.
 - Large amount of observational studies reporting patient satisfaction with cannabinoid treatments.

Benefits

- Chemotherapy Induced Nausea and Vomiting:
- Most studies look at dronabinol and nabilone.
- In adults these are highly effective. Better than placebo, and similar to conventional antiemetics.
 - Rates of adverse effects higher, but still preferred by patients over other antiemetics. Results in peds not as conclusive.
- No good studies in literature looking at whole plant *Cannabis* or CBD extract. Lots of anecdotal evidence.

Benefits

- MS related spasticity:
- -Pooled analysis of 3 trials evaluating nabiximol or nabilone vs placebo. Found to improve patient self-reported spasticity scores. Results were statistically significant.
 - When Ashworth scores were evaluated in different pooled analysis of 5 studies, score improvements were found vs placebo, but not statistically significant.

Limited evidence for benefit: mixed findings, uncertainty, high amount of bias or confounders in studies

- Appetite stimulation and weight gain, PTSD treatment, anxiety treatment, Tourette syndrome treatment

Inconclusive in determining benefit:
due to mixed findings, poor studies,
lack of data.

- -Cancer curative treatment, Epilepsy treatment (as a whole), treatment of neurodegenerative disorders, treatment of IBS, addiction therapy (primarily opioid and nicotine).

Benefits

- In treatment resistant epilepsy (primarily Dravet syndrome and Lennox-Gastaut), CBD has shown some benefit for seizure control as an adjunctive medication to traditional antiepileptics. No evidence available with CBD as sole treatment. Most studies reported fatigue and somnolence as main adverse effects.

Summary of Benefits

- Some modest benefits, studied and noted mostly with purified extracts and current FDA approved formulations. Severe need for more high quality studies to get a better understanding of whole plant marijuana effects.
- There is concern regarding medical use of marijuana, since it has not undergone the same FDA scrutiny, regulation, and approval that most drugs have.

Risks of use of *Cannabis* and its derivatives

Risks

- Intoxication/side effects (or intended effects) of use:
- Euphoria, tachycardia, tachypnea, hypertension, dry mouth, nystagmus, ataxia, increased appetite, slurred speech, dizziness, tiredness, short term cognitive impairment persisting even 24 hours after use, psychosis/hallucinations. Some will experience dysphoria, anxiety, or panic.
- Acute use of *Cannabis* results in impairment of every important metric related to the safe operation of a motor vehicle. Multiple studies demonstrate increased risk for MVA with acute marijuana intoxication.

Risks

- Dosing and effect is difficult to determine in recreationally available products. There are no well-demarcated levels of how dosages may affect an individual, thus one easily may ingest or use more than intended.
 - Extremely high doses are needed to cause severe adverse effects
 - Per 2018 WHO report:
 - The risk of a fatal cannabis overdose is extremely small. The dose of THC that would be a fatal dose in humans, extrapolated from animal studies, is between 15 g and 70 g.

Risks

- Some edibles are difficult to distinguish from normal foods and candies.
- Overdoses in children who have ingested products: sleepiness, euphoria, irritability, delirium, slurred speech, depressed mental status. Coma with apnea, or depressed respiratory status in large overdoses (typically seen at extremely high doses, around 300 mg THC).
- Pediatric exposures occur more frequently in states with legalized recreational use.

Risks

- Respiratory Diseases: mainly occur with smoked (and possibly vaporized) products.
- COPD: small amount of evidence for increased risk after controlling for tobacco use.
- Asthma: no association for development of asthma. Certainly could trigger.
- Bronchitis, general respiratory symptoms: Long term Cannabis smoking causes symptoms of bronchitis and microscopic injury to bronchial lining cells. There is moderate evidence for improvement in symptoms after cessation.
- Lung cancer: at this time, it is unclear from the current evidence if smoking marijuana is a risk factor

Risks

- CV Risk:
- Evidence examining the effect of marijuana on cardiovascular risk factors and outcomes, including stroke and myocardial infarction, is insufficient. (Ravi)
- WHO report states some evidence for intoxication triggered events.
- Long term heavy use potentially triggers stroke and MIs in young users (<50 years old).

Risks

- Psychosocial:
- Cognitive deficits with acute use. Impaired learning, memory, and attention related to recent cannabis use, even as long ago as 24 hours. Decrease motivation during intoxication.
- Increasing evidence that these deficits persist even beyond the initial 24 hours.
- Effect probably decreases after 72 hours abstinence.
- In adolescents that use marijuana there is a negative impact on educational attainment, lifetime achievement in employment, income, and social relationships and roles. (Fitzcharles)

Risks

- Mental Health and Substance Abuse:
- Acute psychotic episodes with acute use. These are becoming more frequent, related to increasing THC concentrations.
- Increased risk of schizophrenia, especially when use initiated at a young age, and frequent users.
- Likely increased risk for social anxiety disorder
- Associated with development of suicidal thoughts, causality not established
- Cannabis use associated with increased risk for abuse of other substances.
 - In one study, approximately 1/4 of chronic pain patients using medical cannabis were high risk alcohol drinkers.

Risks

- Prenatal, perinatal, neonatal risks:
- Some dispensaries in Colorado were found to be recommending *Cannabis* products for morning sickness treatment. Most recommending edibles.
 - Unregulated employee training and no regulations about recommendations or advice that employees can give.
 - Studies have shown that only around 20% of dispensary employees have some sort of medical or scientific training. 71% of employees giving advice based it on personal experience only.

Risks

- Prenatal, perinatal, neonatal risks:
- Later in life, children show: low birth weight; impaired attention, learning, and memory; impulsivity and behavioral problems; higher likelihood of using marijuana as an adult
- Just released study by Baker, et al, shows that newborns who are exclusively breast fed will ingest about 2.5% of the THC that the mother takes in when using marijuana (primary method was smoking). Unfortunately the long term affects of this are poorly understood.

Risks

- Cannabis Use Disorder: Specific DSM-V diagnosis, similar to other substance use disorders.
- A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
 1. Cannabis is often taken in larger amounts or over a longer period than was intended.
 2. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.
 3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
 4. Craving, or a strong desire or urge to use cannabis.
 5. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
 6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
 7. Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
 8. Recurrent cannabis use in situations in which it is physically hazardous.
 9. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.
 10. Tolerance, as defined by either of the following:
 - a. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect.
 - b. Markedly diminished effect with continued use of the same amount of cannabis.
 11. Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for cannabis.
 - b. Cannabis (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

Risks

- Cannabis withdrawal syndrome:
 - constellation of signs and symptoms occurring within 1 week after abrupt reduction or cessation of heavy or prolonged *Cannabis* use. Irritability, anger, anxiety, depression, sleep disturbances, abdominal discomfort, headache, muscle tremor, or muscle twitching.

Risks

- Cannabis Hyperemesis Syndrome.
 - Cyclic vomiting-like condition associated with long term and high dose cannabis use. Those affected self-treat with repetitive hot water bathing behavior during vomiting cycles.

Opioids and *Cannabis*

- Effects of concomitant THC and opioid use:
 - Shared effects: antinociception/analgesia, hypothermia, inhibition of locomotor activity, hypotension, sedation
 - THC enhances the effects of opioids
 - THC has some action at opioid receptors
 - THC stimulates the release of endogenous opioids
 - THC enhances the acute analgesic effect of opioids
- Side effects are additive. Increased severe adverse events.
- In patients using opioids and *Cannabis*, serious adverse events are as high as 20/100 patient-years.
- Study of *Cannabis* plus opioids: 44% of those on opioids had discontinued their opioids at the end of the 6 month study period.

Positions statements

- AAFP
- **Medical Use of**
- The AAFP recognizes that there is support for the medical use of marijuana but advocates that usage be based on high quality, patient-centered, evidence-based research and advocates for further studies into the use of medical marijuana and related compounds. The AAFP requests that the Food and Drug Administration change marijuana's classification for the purpose of facilitating clinical research. This process should also ensure that funding be available for such research.
- The AAFP also recognizes that some states have passed laws approving the medical use of marijuana; the AAFP does not endorse such laws. The AAFP encourages its members to be knowledgeable of the laws of their states and consult with their state medical boards for guidance regarding the use of medical marijuana.
- **Recreational Use of**
- The AAFP opposes the recreational use of marijuana, however supports decriminalization of the possession and personal use of marijuana. The AAFP recognizes that several states have passed laws approving limited recreational use or possession of marijuana and therefore advocates for further research into the overall safety and health effects of recreational use as well as the effects of those laws on patient and societal health.

Positions statements

- ACOG

- The American College of Obstetricians and Gynecologists recommends the following:
 - Before pregnancy and in early pregnancy, all women should be asked about their use of tobacco, alcohol, and other drugs, including marijuana and other medications used for nonmedical reasons.
 - Women reporting marijuana use should be counseled about concerns regarding potential adverse health consequences of continued use during pregnancy.
 - **Women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use.**
 - **Pregnant women or women contemplating pregnancy should be encouraged to discontinue use of marijuana for medicinal purposes in favor of an alternative therapy for which there are better pregnancy-specific safety data.**
 - **There are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged.**

Summary

- Complex system with many exogenous cannabinoids from *Cannabis* plants. Many ways that these products are being used. Multitude of dosage forms, dosages not well understood or standardized.
- Some evidence possibly for management of pain, nausea and vomiting, MS related spasticity. Limited evidence for benefit in appetite stimulation, PTSD, anxiety, Tourette.
- Lots of risks, poor understanding of whole plant effects, poor understanding of effects from most common ways of use.

Needs for further study

- The list goes on and on...

How to counsel patients

- Evidence for benefits from *Cannabis* limited, poorly understood.
- Lots of side effects of use, especially with whole plant material. Possibly long term detrimental effects.
- Not a replacement for opioids, still plenty of side effects, risk for addiction and use disorder. Avoid using marijuana+opioids, benzos, or other controlled substances.
- Probably better treatment options for many of the conditions for which patients may want to use *Cannabis*, at this time.
- A last resort for most things
- Still illegal in Idaho, can't protect the patient from law enforcement if using illegally. Best not to risk it.

Amusing, yet concerning...

Obstetrics: Original Research

Recommendations From Cannabis Dispensaries About First-Trimester Cannabis Use

Betsy Dickson, MD, Chanel Mansfield, MPH, Maryam Guiahi, MD, MS, Amanda A. Allshouse, MS, Laura M. Borgelt, PharmD, Jeanelle Sheeder, PhD, Robert M. Silver, MD, and Torri D. Metz, MD, MS

OBJECTIVE: To characterize recommendations given to pregnant women by Colorado cannabis dispensaries regarding use of cannabis products for nausea during the first trimester of pregnancy.

METHODS: This was a statewide cross-sectional study in which advice about cannabis product use was requested using a mystery caller approach. The caller stated she was 8 weeks pregnant and experiencing morning sickness. Dispensaries were randomly selected from the Colorado Department of Revenue Enforcement Division website. The primary outcome was the proportion of marijuana dispensaries that recommended a cannabis product for use during pregnancy. We hypothesized that 50% of dispensaries would recommend use. A sample size of 400 was targeted to yield a two-sided 95% CI width of 10%. Secondary out-

comes included the proportion endorsing cannabis use as safe during pregnancy, specific product recommendations, and encouraging discussion with a health care provider. Recommendations were compared by licensure type (medical, retail, or both) and location (rural vs urban).

RESULTS: Of the 400 dispensaries contacted, 37% were licensed for medical sale ($n=148$), 28% for retail ($n=111$), and 35% for both ($n=141$). The majority, 69% (277/400), recommended treatment of morning sickness with cannabis products (95% CI 64–74%). Frequency of recommendations differed by license type (medical 83.1%, retail 60.4%, both 61.7%, $P<.001$). Recommendations for use were similar for dispensary location (urban 71% vs nonurban 63%, $P=.18$). The majority (65%) based their recommendation for use in pregnancy on personal opinion and 36% stated cannabis use is safe in pregnancy. Ultimately, 81.5% of dispensaries recommended discussion with a health care provider; however, only 31.8% made this recommendation without prompting.

CONCLUSION: Nearly 70% of Colorado cannabis dispensaries contacted recommended cannabis products to treat nausea in the first trimester. Few dispensaries encouraged discussion with a health care provider without prompting. As cannabis legalization expands, policy and education efforts should involve dispensaries.

(*Obstet Gynecol* 2018;131:1031–8)
DOI: 10.1097/AOG.00000000000002619

Marijuana use in pregnancy may have adverse effects on the fetus, including fetal growth restriction and long-term neurologic consequences.^{1,2} The American College of Obstetricians and Gynecologists states, “obstetrician-gynecologists should be discouraged from prescribing or suggesting the use of marijuana for medicinal purposes during pregnancy, conception, pregnancy, and lactation.”³

Expanding legalization may increase use among pregnant women and may be accompanied by

From the University of Colorado School of Medicine and the Colorado School of Public Health, Aurora, Colorado; the University of Utah Health, Salt Lake City, Utah; and Denver Health and Hospital Authority, Denver, Colorado.

Dr. Metz is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development under award number 5K12HD001271-18. This project was also supported by the Colorado Clinical and Translational Sciences Institute with the Development and Informatics Service Center under award number U11 RR025780. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Presented as a poster at the Society for Maternal-Fetal Medicine’s 38th Annual Pregnancy Meeting, January 29–February 3, 2018, Dallas, Texas.

Each author has indicated that he or she has met the journal’s requirements for authorship.

Corresponding author: Torri D. Metz, MD, MS, 777 Bannock Street, MC 0660, Denver, CO 80204; email: torri.metz@dhha.org

Financial Disclosure
Dr. Borgelt received grant funding from the Colorado Department of Public Health and Environment (CDPHE) for a study evaluating the use of cannabidiol for the treatment of refractory pediatric epilepsy. Additionally, she has served on seven different working groups for the Colorado Department of Revenue and CDPHE regarding use of cannabis and patient safety. The other authors did not report any potential conflicts of interest.

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ISSN: 0029-7844/18

VOL. 131, NO. 6, JUNE 2018

OBSTETRICS & GYNECOLOGY 1031

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Box 2. Representative Quotes From Cannabis Dispensary Employees in Response to Phone Script Questions*

“I’m calling because I’m 8 weeks pregnant and nauseated. Are there any products that are recommended for morning sickness?”

- “Let me call my daughter, she just had a baby, call me back in 5 minutes.”
- “On the package it says do not consume while pregnant—there may be health risks associated with this product if you are pregnant, breastfeeding, or planning on becoming pregnant. You are welcome to come to the shop to see if we can find something, but I think most of the labels are going to be like that.”
- “Have you talked to your doctor? I do not want to recommend anything you know. I know what would help with nausea, but I do not think I could legally recommend anything for someone that is pregnant, but I could recommend something for nausea do they still let you purchase while you are pregnant?”
- “I cannot give medical advice; look it up and then call me and I’ll see if I have the product, but we do have CBD and weed in stock.”

Why is the product recommended or not recommended?

- “All the products say it is not recommended for pregnant women use; they just do not know what it could do to the fetus there is not enough studies out there. It is a drug, so probably not the best thing for you when you are pregnant.”
- “Technically with you being pregnant, I do not think you are supposed to be consuming that, but if I were to suggest something, I suggest something high in THC.”
- “Legally cannot provide a recommendation.”
- “Need a doctor’s recommendation first.”
- “Edibles would not hurt the child; they would be going through your digigestion [digestive] tract.”
- “They have been doing studies; as long as you are not heavily harshly smoking like the smoke I think that is the only way it could physically damage the baby, cause you are inhaling smoke.”

Recommendations on frequency

- “In the context of edibles, start with a low dose and see how it works out for you because those types of things would, um, not cross the blood–brain barrier so even if you have got the CBDs and the other good parts of the plants would get in your baby’s blood system but the psychotropic properties, the THC molecule, would not get near your baby, so basically would not be getting your baby stoned.”
- “Before your first trimester. Second trimester you do not want to overconsume. When I was pregnant and started to feel a little nausea coming on, I did not smoke more than two times a day.”
- “I am not sure, I do not really know, I am not really too familiar with this, cause I do not want to give you the wrong information and find out it can be harmful to your baby, so I do not want to tell you the wrong thing; just one of my coworkers, she was pregnant and she was using flower and vaping.”

Responses regarding speaking with a health care provider

- “I think that would be a smart choice. Try for someone that is liberal or pro-cannabis. The others are not fully educated on the benefits of cannabis and will tell you to stay away, but always check with a medical professional.”
- “I do think you should talk to your doctor at your discretion about it. I know there are some doctors that might be really uncomfortable with that. I do think that it is a medical professional’s responsibility to be open to talking with their patient...”
- “The doctor will probably just tell you that ‘marijuana is bad for kids and will just try pushing pills on you.’ Maybe you have a progressive doctor that will not lie to you. All the studies done back in the day were just propaganda.”
- “Google it first. Then if you feel apprehensive about it, you could ask.”
- “Most of them out here tell them not to smoke weed. Even the cancer doctors. It is so messed up. I do not know how the baby doctors work; if they are chill or not. Just do not go stoned when you talk to them.”
- “No, because they will test you when the baby is born and can get child protective services involved; that is just the unfortunate honest truth.”
- “In the state of Colorado you are protected, so it is not something you have to bring to their attention...they are not gonna call CPS like they would have 10 years ago if you have MJ in your system.”

Is cannabis safe to take during pregnancy?

- “Different people opinions, kind of like alcohol; I used to be a bartender and it is legal to serve someone who is pregnant because it is up to them so you know. I am not here to tell you you should or should not use, does that make sense. I do know a lot of people that do use cannabis during their pregnancy though and for what they have found, there has not been side effects that they can see.”
- “I know a lot of doctors are recommending marijuana nowadays.”
- “We have a girl that comes in and she is probably 6 months pregnant and she smokes bud but she does not smoke it as much as she did but she still does...she said her doctor said it was ok...she said the doctor said that but I am not a doctor...I know aspirin is ok for babies and that is pretty much what you are getting is an aspirin that is probably better.”

CBD, cannabidiol; THC, tetrahydrocannabinol; CPS, child protective services; MJ, slang for marijuana.

*The response may not be directly associated with the direct question as a result of the open-ended nature of the question.

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Amusing, yet concerning...

- Excerpts from Colorado study regarding 1st trimester advice from dispensaries:
 - “I’m calling because I’m 8 weeks pregnant and nauseated. Are there any products that are recommended for morning sickness?”
 - “Let me call my daughter, she just had a baby, call me back in 5 minutes.”
 - Why is the product recommended or not recommended?
 - “Edibles would not hurt the child; they would be going through your digestional [digestive] tract.”
 - Responses regarding speaking with a health care provider
 - “The doctor will probably just tell you that ‘marijuana is bad for kids and will just try pushing pills on you.’ Maybe you have a progressive doctor that will not lie to you. All the studies done back in the day were just propaganda.”
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Questions?

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